BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

Vol. XV.—No. 164.] BALTIMORE, NOVEMBER, 1904. [Price, 25 Cents.

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AN EARLY CASE OF ULCER OF THE STOMACH.[1]

By Joseph C. Bloodgood, M. D., Baltimore.

(*Single. Situation: Lesser Curvature, 4 cm. from Pylorus. Clinical and Gross Pathological Diagnosis: Doubtful. Operation: Pylorectomy. Recovery.*)

The case which I am about to report is of interest because of the short duration of the symptoms, 3 weeks, and the difficulty of making a positive diagnosis of the indurated tumor situated in the lesser curvature of the stomach.

Clinical History.—The patient was a white male, 33 years of age. Eight years ago this patient came under my observation with a sinus communicating with one of the ribs on the left side. The history suggested tuberculosis. Slight pain had been the symptom of onset, some 4 months ago. Following this the formation of a chronic abscess, which ruptured spontaneously two months ago. At the operation the sinus was lined by hemorrhagic granulation tissue, situated on a very fibrous base. The sinus had two or three branches; one extended to the fifth rib, but the bone lesion had healed. Microscopically we were unable to demonstrate tubercle bacilli, or the histological lesion of tuberculosis.

Since this operation the patient has been well until three weeks ago.

His occupation is that of a laborer in an iron foundry. His daily work is very hard and he is exposed to extreme degrees of heat. He states, however, until three weeks ago he experienced no pain or discomfort in the abdomen, and no indigestion. He thinks perhaps that for a few months previous his appetite was not as good as formerly.

Present Illness.—Three weeks ago (he is quite positive as to the time) he began to suffer discomfort in the epigastrium. The area of discomfort was about 8 x 8 cm., beginning below the ensiform cartilage. The pain was not referred. All this discomfort, which has been pretty constant, was worse after eating. After a few days he began to vomit at night, vomiting being rarely present except at this time. The vomitus seldom contained undigested particles of food; was moderate in amount, usually watery in consistency, and with the acidity characteristic of ordinary gastric juice. The discomfort in the epigastrium continued in spite of the fact that the patient discontinued work and practically stopped eating solid food. After restricting his diet the amount of material vomited was less. A day, however, did not pass in which there was not one or more attacks of vomiting.

The patient is a spare, muscular man with no excess of fat. He thinks, however, that he has lost some flesh, but not sufficient to be noticeable.

Examination.—Color good, tongue clean. Facial expression gives no evidence of pain. The patient states that he is suffering from pain in the epigastrium, and places his hand midway between the ensiform cartilage and umbilicus. The pain is present equally on both sides of the medial line. Inspection, negative. Practically no subcutaneous fat.

Palpation.—There is perhaps slight resistance of the recti muscles above the umbilicus, but none of the lateral abdominal

[1] Reported before the Johns Hopkins Hospital Medical Society, May 16, 1904.

muscles beneath the ribs. In spite of this slight resistance, fairly deep palpation is possible, but as one is unable to palpate either the pulsations of the abdominal aorta or the spinal column a small tumor could easily be present.

Percussion.—On percussing the epigastrium I was at once struck with the absence of the usual epigastric tympany. The entire epigastrium corresponding to the usual position of the normal stomach was flat except a small triangular area situated to the left of the median line along the border of the ribs, beginning at the ensiform cartilage. This note of tympany shifted to the right of the median line when the patient was turned on his left side, and moved slightly beneath the ribs when the patient was turned on his right side. This clinical sign suggested an increase in the amount of gastric juice.

The patient was admitted to the Union Protestant Infirmary on April 19, 1904, put to bed and given by mouth nothing but boiled water and albumin. Unfortunately, an examination of the gastric contents was not attempted until two days later, and at this time none of the contents of the stomach could be obtained. However, as at the operation, after three days of restricted diet, and after 24 hours of practically no fluid, there was found in the stomach about 200 cc. of residual fluid, lighter in color than normal gastric juice, with slight increase of acidity in which hydrochloric acid was present.

Clinical Diagnosis.—The brief duration of the disease in a man of 33, the distinct local symptoms, and the absence of a history of alcoholic indulgence, pointed with a good deal of certainty either to an ulcer or a cancer. In my judgment there were sufficient indications for an exploratory laparotomy. I explained to the patient, it was probable that under rest in bed and rectal feeding he would improve if the disease were an ulcer; but there were great probabilities of a recurrence of the symptoms; that if he subjected himself to operation the risk would be slight and the loss of time less, and a far better assurance of a perfect cure than after medical treatment. In addition, if the disease proved to be cancer, his chances of a cure would be greatly increased by an immediate operation at this early stage. The patient chose to undergo an operation.

Operation.—April 22, 1904. Anesthetic, ether. The anesthetic was well taken and there were no complications. The abdomen was opened through the belly of the right rectus muscle. There was very little subcutaneous fat. On opening the abdomen I was struck with the absence of pro-peritoneal fat so frequently observed in the epigastrium, and scanty fat in the omentum. The incision exposed at once the pyloric end of the stomach. One could see at the lesser curvature, about 4 cm. from the pylorus, a swelling involving the anterior portion of the stomach. The center of the tumor corresponding to the attachment of the lesser omentum was umbilicated. The peritoneum and fatty tissue in the omentum were retracted in this direction, a condition most frequently observed in the connective tissue around carcinoma, but one which I have observed in the omentum, chronically inflamed and adherent to an inflamed gall bladder or appendix. The peritoneum over the anterior portion of the tumor was darker in color than that over the normal stomach, and looked edematous. There was no special engorgement of the vessels over the tumor. On palpation the tumor was hard as a scirrhus carcinoma, and apparently disk-shaped, about 3 cm. in diameter and 1 cm. in thickness. The induration involved chiefly the anterior wall of the stomach and extended slightly to the posterior wall. The fat in the lesser omentum was indurated and adherent to it. A most careful palpation gave me an impression that I was dealing with a carcinoma. However, invaginating the normal anterior wall of the stomach against the mucous membrane surface of the tumor, and holding the tumor with the left hand, I could place the index finger of the right hand in a cavity which easily admitted the end of the finger. The wall of this cavity felt smooth and hard. I could palpate the smooth, slightly elevated mucous membrane about this cavity, which mucous membrane was adherent to the surrounding tumor mass. After this examination it seemed to me that the characteristics could be explained more easily by the theory of a simple chronic ulcer surrounded by a zone of inflammatory tissue. In carcinoma secondary to a simple ulcer in the majority of cases one gets a history of disease of much longer duration, and as a rule the ulcer is not so deeply excavated, and has not such a smooth surface. Inspection and palpation demonstrated the absence of enlarged glands in the lesser curvature. However, in the greater curvature, beginning at the pylorus and extending half the length, there were a number of enlarged glands, the largest 1 cm. in diameter, situated near the pylorus. This gland was removed, and on section showed no evidence of metastasis. It was soft and did not show much increase in fibrous tissue. As a rule a gland of this size would, if it contained cancer nests, have a distinct naked-eye appearance.

Although the gross appearance and the findings on palpation were in favor of an ulcer, I considered there was sufficient doubt to justify a complete operation. A resection was done in the ordinary manner. On account of the probable character and situation of the tumor, the division was made between the pylorus and duodenum. At the lesser curvature the stomach was divided about 4 cm. from the tumor, at about the position of the anterior branch of the gastric artery. From this point the incision extended at an angle a little to the right of the vertical line, so that less of the greater curvature was removed than is usual in carcinoma. With the greater curvature a part of the omentum and all the enlarged glands were removed. After removal of this portion of the stomach it was found that the stomach at the position of the greater curvature could be sutured so easily and without tension to the duodenum that the original method of Billroth was employed. In closing the stomach and in performing the end-to-end anastomosis between the stomach and duodenum, two rows of sutures were employed, continuous catgut passing through all the walls, reinforced by interrupted mattress sutures of fine black silk. The abdominal wound was closed without drainage. See Figs. 1 and 2, Plate XXIX.

Convalescence.—After operation there were no complications except slight nausea and vomiting up to the tenth day, when the patient was given much liquid by mouth. After the

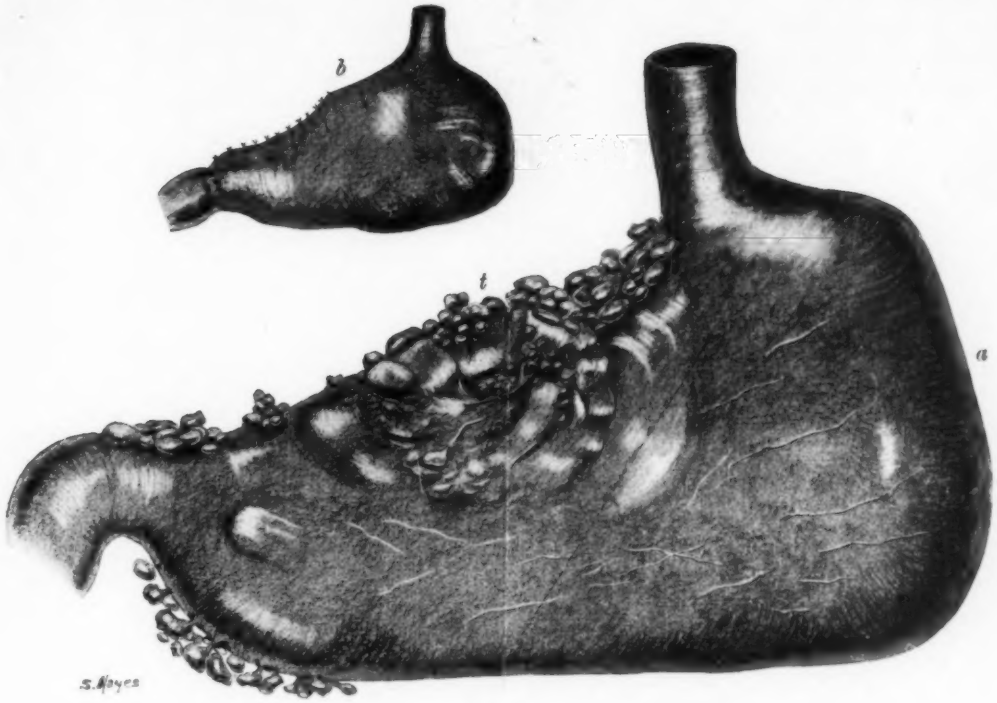

FIG. 1.

FIG. 2.

FIGURE 1. (*a*) Stomach before operation. (*t*) Visible and palpable tumor.
(*b*) Stomach after operation.

FIGURE 2. (*a*) Inside view of stomach showing ulcer.
(*b*) Section through stomach wall and base of ulcer.

second week he retained food taken by the mouth, which was gradually increased.

The wound healed per primam.

NOTE.—July 26, 1904. It is three months since operation. The patient has been at work for six weeks, has gained 30 lbs. in weight and states that he suffers absolutely no epigastric distress. He has an excellent appetite and can eat anything he wants. (Oct. 20, 1904. He remains well.)

Gross Pathology.—The naked-eye appearances are characteristic of an excavated chronic ulcer. On inspecting the tumor from the stomach side a cavity is seen which about admits the end of the index finger. The mucous membrane surrounding it, appears normal. It extends a little over the edge of the cavity, becomes thin, ends abruptly in a smooth finely granular granulation tissue lining the remainder of the cavity. The mucous membrane about the cavity is a little elevated. There is no evidence of any attempt at epithelial growth over the ulcer surface. On section one sees beneath the surrounding mucous membrane and the surface of the ulcer a wide zone of dense white fibrous tissue, which extends between the mucous membrane and peritoneum, and between the ulcer surface and the peritonum. In this fibrous tissue one can recognize nothing of the muscular coats of the stomach. There is no increase in vascularity. The distance between the mucous membrane and border of the ulcer and the peritoneum is about 1.5 cm.; between the base of the ulcer and the peritoneum about 4 mm.; so that there was but 4 mm. of connective tissue preventing a perforation. The hemorrhagic granulation tissue lining the surface of the ulcer was as a rule about 1 to 2 mm. in depth, except at the base, where a mass of finely granular and hemorrhagic connective tissue extended to the peritoneal coat. This point to the naked eye had a suspicious appearance of beginning carcinoma. The peritoneum of the lesser curvature extending over the tumor, contained a moderate amount of infiltrated fat adherent to the zone of inflammatory tissue about the ulcer. No lymph glands were to be made out in this infiltration. The remainder of the stomach excised and that left after excision was, after most careful inspection, found to be normal.

Microscopic Study.—Sections showed nothing but chronic inflammatory tissue. The surface of the ulcer has a narrow zone in which the connective tissue is very cellular and somewhat vascular. Beneath the mucous membrane surrounding the ulcer the connective tissue is very fibrous, infiltrating in all directions. The mucous membrane of the stomach ends abruptly. The only change to be noted is atrophy of the glands and slight lymphoid cell infiltration. There is no atypical growth of epithelium of the mucous membrane or its glands at the edge of the ulcer, and no hypertrophy of the glands beyond. The large lymph glands in the greater curvature show no evidence of metastasis, and but slight chronic inflammation.

This case is reported because of the difficulty in making a positive diagnosis at the exploratory operation, and to record in detail the naked-eye appearance with a hope that in the future similar cases can be recognized with some positiveness.

During the last year I have devoted considerable time to a study of the literature of diseases of the stomach, the most important of which are gastric ulcer and carcinoma. In International Clinics, Vol. I, for 1904, I have attempted to give a short résumé of this literature. The present almost unanimous opinion of surgeons favors exploratory operations in doubtful cases. Delay for a positive diagnosis between cancer and ulcer is not justifiable. There is little or no hope for a cancer of the stomach in the late period of the disease when the diagnosis is indicated by the examination of the gastric secretion. A tumor is a positive indication for operation; an absence of tumor is never a contraindication to operation. In young anæmic girls or in women exhibiting the typical clinical picture and gastric secretion of a simple ulcer an operation is only indicated when in addition there is hemorrhage or signs of gastric adhesions or pyloric obstruction, or in the event of failure of or only temporary relief from medical treatment. The so-called gastric neuroses, which as a rule are not difficult to differentiate from ulcer or cancer, should not be subjected to operation. If one takes this view, the diagnosis between ulcer and cancer cannot be made with certainty clinically. After the stomach is exposed, in a number of cases, the diagnosis of ulcer should not be difficult, and gastroenterostomy should be done. In other cases we can be quite certain that we are dealing with a carcinoma. If the operation is performed early, at least until our experience increases, I am inclined to think that there will be a large number of doubtful cases. These may be divided into two groups. In the first the indurated tumor is either freely movable or only slightly adherent. In this group complete resection should be performed. This operation gives the only hope for cancer, and as these patients are usually in good condition the mortality for gastrectomy, if it is an ulcer, should be but little if any greater than for gastroenterostomy. In the second group, the indurated tumor is so adherent to the surrounding structures that if the lesion were carcinoma it is past the hope of complete removal. For this reason gastroenterostomy should be performed. If the lesion is an ulcer, there will be permanent relief.

Future progress in surgery of the stomach depends upon the harmonious co-operation of the physician and surgeon. The problem of the physician is to secure a more positive differential diagnosis between ulcer and cancer in its earlier stages by the chemical study of gastric secretion. The problem for the surgeon is the differential diagnosis between ulcer and cancer at the exploratory operation.

DISCUSSION.

DR. HALSTED mentioned a case of carcinoma of the stomach which showed the difficulty of making a diagnosis. There had been a history of gastric ulcer extending over a period of three years. In this case a mass could be palpated before the operation through the abdominal parietes and enlarged glands could be detected along the duodenum and over the head of the pancreas. The distribution of the tissue was so different from

what one would expect in a simple inflamed gland, he felt justified in making the operation. The report from the laboratory showed that it was a solid carcinoma. The patient recovered from the operation, has since gained about 30 pounds in weight, and his symptoms have disappeared.

Dr. Bloodgood.—I wish to ask Dr. Emerson if he has had early cases of cancer, cases proven at autopsy or operation to be cancer, in which hydrochloric acid was still present, where there would be a sufficient difference to aid one in making a diagnosis from ulcer? There must be such a stage in cancer. Is there anything in the chemistry of the subject at this stage that would help us in differentiating?

Dr. Emerson.—Cases of early cancer with abundant hydrochloric acid are not rare. One point in the early diagnosis of such cases is that if repeated examinations of the gastric juice be made the acid will be found very variable, or much more so than in simple ulcer, for early in the disease the amount found depends not only upon that secreted but also that neutralized by basic bodies furnished by, or at least depending upon, the presence of the cancer.

This variability in the amount of acid was present in Dr. Halsted's case, but enough examinations had not been made to demonstrate the point well.

Dr. Bloodgood.—That corresponds with the only two early cases that I know of in the literature that have been operated on and proven to be cancer. Where there was a very careful examination made every day for weeks, this change in the hydrochloric acid was noted. These are the only two cases, however, that I could find.

THE USE OF THE CYSTOSCOPE IN CASES OF PROSTATIC HYPERTROPHY.[1]

A Presentation of Charts to Facilitate the Interpretation of the Cystoscopic Views.

By Hugh H. Young, M. D.,

Associate Professor of Genito-Urinary Surgery, The Johns Hopkins University.

Since the beginning of cystoscopy it has been considered extremely difficult to determine with the cystoscope the exact size and contour of the intravesically hypertrophied prostatic lobes. Several cystoscopists have even asserted that it was impossible to arrive at an accurate idea of the conditions present. On the strength of these acknowledgments of failure, several surgeons have declared the cystoscope both useless and dangerous in cases of prostatic hypertrophy.

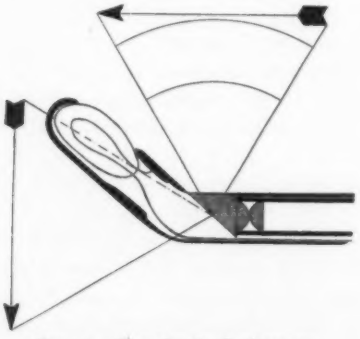

Fig. 1.—The simple Cystoscope.

Realizing the difficulties, but appreciating from numerous experiences the great advantage of the knowledge obtained by cystoscopic examination before operation in these cases, I set to work several years ago to devise a means of recording the views obtained with the cystoscope, so that we might formulate rules for their correct interpretation, and it is my purpose to-day to present the results of this study.

As shown in Fig. 1, in the plain cystoscope the rays of light are deflected 90° by the rectangular prism, and the line of vision is therefore at right angles to the shaft of the instrument. The base and lateral walls of the bladder, being more or less parallel to the shaft of the cystoscope, are easily viewed by the simple cystoscope. The anterior wall can be seen well only by considerably depressing the handle of the cystoscope, but in order to see the margins of the prostatic orifice it is necessary to withdraw the cystoscope until the prism enters the prostatic orifice (Fig. 8), when, for the first time, the margin comes into the field of view. But then, owing to the close proximity of the prism to the object viewed, there is considerable magnification produced. The picture thus obtained is as represented in Fig. 2, a segment constituting about one-sixth of the margin of the orifice. It is therefore necessary to take at least six consecutive views in order to see the entire circumference of the prostatic orifice. Owing to the spherical aberration, which is more or less pronounced near the periphery of the field of the cystoscope, it is better to take eight successive views.

We thus see that the study of normal orifice is beset with difficulties, but when we come to deal with the multitudinous forms of irregular and abnormal orifices produced by hypertrophied prostatic lobes, the chances of error, and difficulties of correct interpretation are greatly increased.

This led the writer to have constructed by Hirschmann in Berlin, in July, 1900, a cystoscope with which he could look almost directly backward so as to view the prostate orifice and

[1] Presented to the American Association of Genito-Urinary Surgeons at Washington, D. C., June, 1903.

its surrounding structures. This cystoscope differed greatly in construction from the cystoscope No. 3 of Nitze, which was

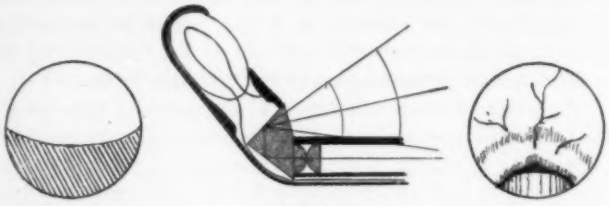

FIG. 2. FIG. 3. FIG. 4.

FIG. 2.—View of margin of prostatic orifice.
FIG. 3.—Author's prostatic Cystoscope.
FIG. 4.—Field of view, prostatic Cystoscope.

intended to view the anterior wall of the bladder, and which I understand was never a mechanical success.

This instrument was demonstrated in 1900 to Professors Nitze and Casper in Berlin, and presented to the meeting of "the American Association of Genito-Urinary Surgeons," May 12, 1903.

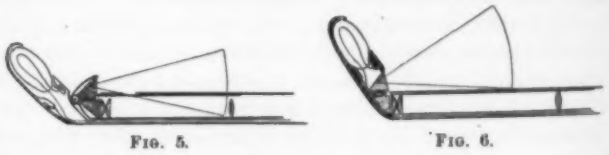

FIG. 5. FIG. 6.

FIG. 5.—Schlagintweit's "Retrograd" Cystoscope.
FIG. 6.—Nitze's "Retrograd" Cystoscope.

Very soon after my publication there appeared in America the "Centralblatt für Harn und Sexual Organs," Heft. IV, 1903, containing a publication by Schlagintweit of his "Retrograd Kystoscop," in which he made use of a different system

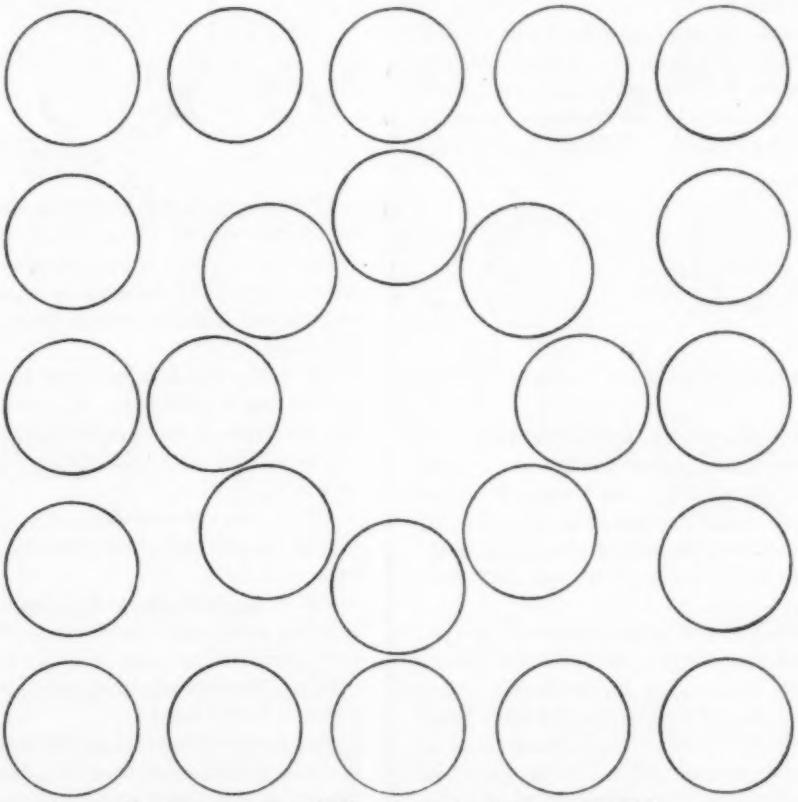

FIG. 7.—Chart for recording views of cystoscopy of prostate.

The design of my cystoscope is shown in Fig. 3. As seen here a prism with two reflecting surfaces was employed to enable the operator to see almost directly backward; the field of vision, as shown in Fig. 4, included the shaft of the instrument, one-half of the margin of the prostatic orifice and the adjacent vesical mucosa. It was thus possible with three or four successive views to examine the surface circumjacent to the prostatic orifice, and to see it without magnification, or aberration.

of prisms and lenses to accomplish the same object, as shown in Fig. 5.

About ten days later there appeared in America the "Monatsberichte für Urologie," Heft V, containing a publication by Schlagintweit of his "Retrograd Kystoscop," in which he made use of a different system of prisms and lenses to accomplish the same object, as shown in Fig. 5.

Nitze has since constructed a "retrograde" cystoscope, using two prisms with an intervening lens, as was done by

Schlagintweit, and only slightly changing the construction of the rest of the instrument (Fig. 6). But after using my own retrograde cystoscope, and later the subsequent models of Schlagintweit and Nitze, I have been forced to abandon all such instruments as entirely unsatisfactory.

This is due to several causes. In the first place, the optics of retrograde cystoscopy is necessarily much less perfect than that of the simple cystoscope. The rays of light must be reflected twice instead of once, losing thereby much light, reducing the size of the field and adding to the distortion and indistinctness of the object viewed.

In the second place, as it is possible to see at one time only a portion of the collarette of prostate surrounding the urethra, it is necessary to make at least four (and generally more) observations in the four cardinal directions to completely view the entire prostatic body, and as each field is inverted, the final interpretation is, in my experience, much more difficult than with the plain cystoscope.

But the most vital objection is that only a small portion of a large intravesical outgrowth can be seen at one time, and it is absolutely impossible to form any conception of the size of the entire mass. And then, since the simple cystoscope is necessary for a careful study of the bladder (I do not find Schlagintweit's satisfactory for this), the extra instrumentation involved in the use of a retrograde instrument is often a great drawback. After experience with my own retrograde cystoscope and an appreciation of the insuperable objections to it, I set about to find some rational means of facilitating the interpretation of the intravesical portion of the enlarged prostate with the simple cystoscope.

FIG. 8.—Position of cystoscope when viewing margin of prostatic orifice.

At first I began to record in circles the different views obtained in the four quadrants around the prostatic orifice. Finding four insufficient, I employed six circles, and then eight circles in which to draw the consecutive pictures. Later it was found advisable to have recorded additional views of the clefts, the relative position of the ureters, or the occasional presence of vesical tumors, calculi, diverticula, etc., so that finally a blank chart, of which Fig. 7 is a copy, was used as a routine in all cases. I have now thus preserved records of over 200 cases, and I wish here to outline the results obtained by a study of these cases, the cystoscopic interpretation of which have been confirmed by operation in many instances.

THE MECHANICS OF PROSTATIC OBSTRUCTION.

Before discussing the cystoscopic findings it may not be amiss to consider the changes which occur at the prostatic orifice as a result of prostatic hypertrophy. I need hardly refer to the multiplicity of forms which prostatic enlargements may present. The prostate may be larger than an orange or not appreciably enlarged at all. It may present little or no change within the bladder, or it may almost fill the cavity. One or all of the respective portions of the prostate may be involved, thus presenting many varieties and forms.

As a rule, the median portion of the posterior commissure (the so-called median lobe), and the lateral lobes are the principal seats of change, but in rare instances the anterior commissure may furnish definite and even great enlargements. The shape of the prostatic orifice depends on the pressure which is brought to bear upon it by single or multiple enlargements of these various portions of the glands.

This is best shown diagrammatically. Thus, Fig. a represents the normal, almost round, prostatic orifice.

Fig. b, the orifice when the two lateral lobes are enlarged. As seen here it is flattened by lateral pressure, and appears as a vertical slit, the extremities or sulci of which are above and below.

Fig. c, the condition produced by the upward pressure of a median lobe hypertrophy. The orifice is an inverted crescent, and the floor of the urethra divided into two channels (Y-shaped). The sulci are obliquely downward and outward on each side.

Fig. d, the opposite effect of a single anterior lobe hypertrophy, the sulci being obliquely upward and outward on each side.

Fig. e, hypertrophy of the median and both lateral lobes. A sulcus above, and one obliquely downward and outward on each side.

Fig. f, the opposite of e, which is produced by an anterior and two lateral lobes.

Fig. g, enlargement of all the four cardinal portions of the prostate—an anterior lobe, two lateral lobes, and a median (posterior) lobe, with 4 sulci as a result.

Fig. h, the median and right lateral lobes confluent, that is, forming a single enlarged mass. Two sulci, one above, one below and to the left.

Fig. i, the opposite, the median lobe being confluent with the left lateral.

Fig. j, the median enlargement in the shape of a bar which is confluent, without intervening sulci, with an enlarged lateral lobe on each side.

Fig. k, an enlargement all around the orifice, leading to circular contracture without sulci.

The above figures cover (diagrammatically, of course) the great majority of the cases of prostatic hypertrophy. There are, of course, certain irregular and bizarre types which are not included, but which can be interpreted by a comparison with the foregoing.

CYSTOSCOPIC PICTURES OF THE VARIOUS FORMS OF HYPERTROPHY.

(a) *The Normal Prostate.*—As remarked above, with the simple cystoscope of Nitze (Fig. 1) the operator sees in a direction at right angles to the shaft of the instrument or the urethra. As seen in Fig. 8, an object such as the prostate which surrounds the shaft of the cystoscope can only be seen when the prism is drawn out close to it, and the image is inverted and magnified. Furthermore, only a small segment of the encircling mass can be seen at a time, so that it is necessary to take at least six separate and successive views in different directions to complete the circumference and see the entire object.

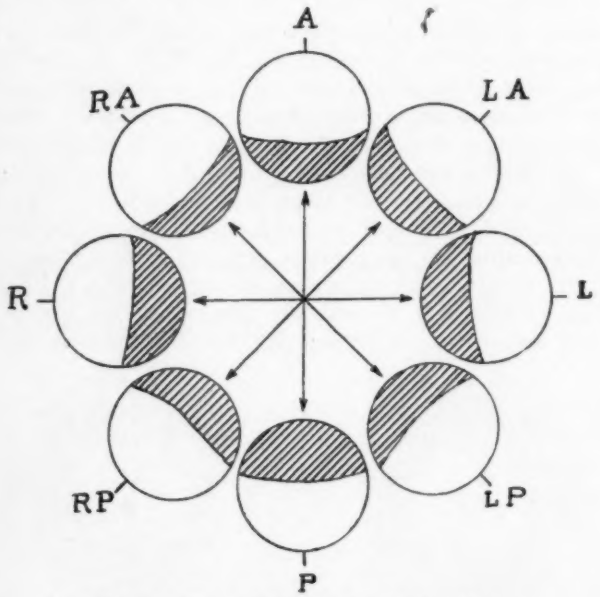

FIG. a′.—Views of the normal prostatic orifice.

The appearance of one such segment (*e. g.*, the anterior) is shown in Fig. 2, the concave line representing the curved segment of the prostatic orifice, the shaded portion of the urethra adjacent to the orifice and the unshaded portion the vesical cavity.

In order to record the entire circumference of the prostatic orifice, it is necessary to have several such circles (preferably 8), and they can be best arranged around a common focal point as shown in Fig. a′. The direction of the circle chosen for record from the central point should correspond to the direction of the beak of the cystoscope. Beginning at one of the cardinal points we are thus able to record the views obtained at intervals of 45° around the entire orifice.

Beginning with A, the beak of the cystoscope is directed upward so as to view the anterior segment of the prostatic orifice. It is then turned 45° to the right and the result recorded in RA. Then 45° further to the right, until the beak is now directed directly to the right lateral lobe, and the picture recorded in R. The process is thus continued, the cystoscope being rotated 45° each time, and the direction of the beak being indicated on the circle which corresponds to that direction, until the entire circumference of the orifice has been viewed and its contour recorded in the series of circles. The record shown in Fig. a′ is taken from a normal prostatic orifice. The resulting pictures, therefore, represent the following segments of the prostatic orifice:

A, the anterior.
RA, the right antero-lateral.
R, the right lateral.
RP, the right postero-lateral.

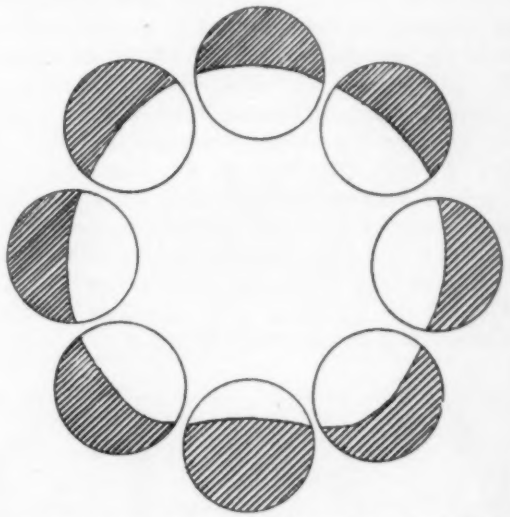

FIG. a″.—The same, inverted, showing outline of magnified normal orifice.

P, the posterior (or middle lobe).
LP, the left postero-lateral.
L, the left lateral.
LA, the left antero-lateral.

As stated above, each of these pictures is an inverted image. If we invert each of the recorded circles, as shown in Fig. a″, we obtain the circular prostatic orifice (magnified, of course).

(b) *The Bilaterally Hypertrophied Prostate.*—As remarked above, the urethra in these cases is compressed by two lateral enlargements and transformed into a vertical slit with a sulcus above and a sulcus below. Between these on each side are more or less rounded lateral lobes. The cystoscopic pictures obtained in such a case (I have selected one in which the exact nature of the enlargement was confirmed at operation) is shown in Fig. b′. (The shape of the orifice as shown in Fig. b above is reproduced in the center. This will also be done in subsequent illustrations.)

We see here a deep sulcus above and below (A and P), while the lateral views show on each side the rounded contour of the lateral enlargement projecting into the bladder. If each of these pictures be inverted, we will have a magnified picture of a prostatic orifice in the shape of a vertical slit with an hypertrophied lateral lobe on each side, as in Fig. b".[1]

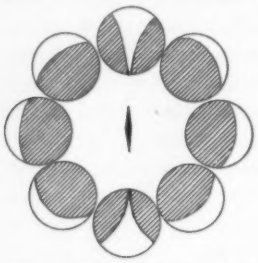

FIG. b'.—Hypertrophy of the two lateral lobes.

FIG. b".

(c) *Small Median Lobe Hypertrophy, with no Enlargement of the Lateral Lobes.*—As seen in Fig. c (reproduced in the center of Fig. c'), the urethral orifice is in the shape of an inverted crescent with sulci on each side of the median lobe. The cystoscopic pictures obtained here as shown in Fig. c'. As seen here there is no change from the normal when looking upward (A) or to either side (R, RA, L and LA), but the three inferior views are greatly changed, P showing a rounded intravesical outgrowth, and RP and LP the sulci which lie on each side of it (the ends of the crescent). Sometimes the median lobe is so small that it is greatly depressed by the cystoscope (which lies against its anterior surface) and the sulci are then seen in R and L as shown in Fig. c".

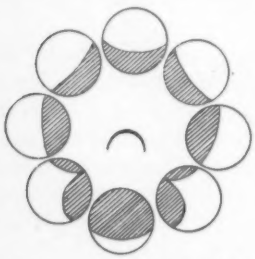

FIG. c'.—Small median lobe.

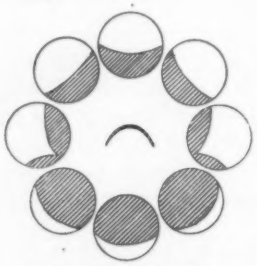

FIG. c".—Median lobe.

Care must be taken not to be deceived as to the size of the lobe. Owing to the immediate juxtaposition of the prism of the cystoscope, such a lobe is always greatly magnified, and the fact that it is seen in 5 fields (R, RP, P, LP and L) should not be taken to mean that it is always large. I have frequently been greatly mistaken as to the size of a middle lobe. By elevating the inner end of the cystoscope, the lobe may often be viewed from a better distance and great magnification avoided. I have numerous records showing Figures c' and c".

(d) *Anterior Lobe Hypertrophy.*—The cystoscopic pictures obtained in such a case are shown in Fig. d'. As there is no lateral or median posterior lobe enlargement, the fields corresponding to these are normal (R, RP, P, LP and P), but the three anterior pictures show the changes which correspond to the crescent-shaped orifice (Fig. d), *viz.:* a rounded, bulging mass in A, and a sulcus to each side of it, in RA and LA.

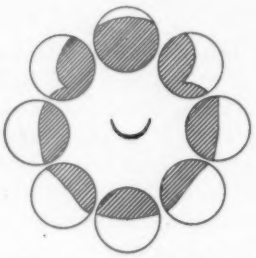

FIG. d'.—Anterior lobe.

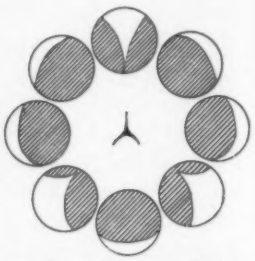

FIG. e'.—Median and bilateral lobes.

(e) *Median and Both Lateral Lobes Enlarged.*—The orifice in this case is in the shape of an inverted Y (Fig. e) (which is a combination of b and c). The cystoscopic pictures obtained are (as might be expected) a combination of those seen in Figs. b' and c', and are shown in Fig. e'. The sulci are seen in A, RP and LP. The median lobe is shown in P and portions of RP and LP, the right lateral lobe in RP, R, RA and the right half of A, and the left lateral lobe in LP, L, LA and the left half of A. If we imagine each of these pictures inverted, we will see at once that we have two lateral lobes separated by an anterior sulcus, and a median lobe separated from each lateral lobe by a sulcus. (As mentioned in (c) the sulci on each side of the median lobe may be seen in R and L.)

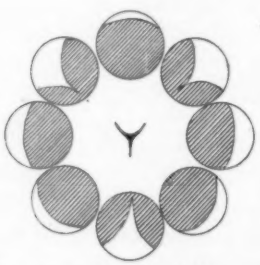

FIG. f'.—Anterior and bilateral lobes.

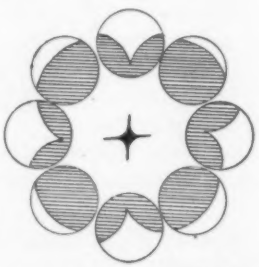

FIG. g'.—Anterior, median and both lateral.

(f) *An Anterior and Two Lateral Lobes.*—The orifice here is a Y, the opposite of (e). The pictures obtained are also the opposite, the clefts appearing in P, RA and LA, and the three lobes in the intervening fields.

(g) *Both Lateral, Median and Anterior Lobe Hypertrophy.*—As stated before, the urethra is here compressed from all four directions and the shape of the orifice is shown in the

[1] This inversion will not give an exactly accurate picture of how the prostatic hypertrophy really looks for several reasons; *viz.:* There is always a certain amount of distortion toward the periphery of every field of the cystoscope, and on that account I have taken eight circles instead of six (which is really all that should be necessary were there no aberration of the image). As a result, these fields overlap. Another reason is that we do not look directly at the orifice, but at right angles to it, and we cannot expect the composite picture to exactly represent the orifice, when viewed from behind.

center of Fig. g'. The pictures obtained in such a case are seen in Fig. g', the clefts appearing in RA, LA, LP and RP, and the intervening lobes in A, L, P and R.

(h) *Median Lobe Confluent with Left Lateral Lobe.*—In such cases the three lobes are each enlarged, but there is no intervening sulcus between the median and right lateral lobes, the two lobes forming one mass. The orifice is shown in Fig. h' (for convenience shown as if viewed from without), the clefts appearing in A and RP. LP shows a confluence of the median and the left lateral lobes without any intervening cleft.

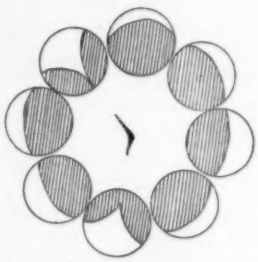

FIG. h'.—Median and left lateral confluent.

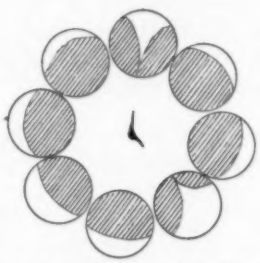

FIG. i'.—Median and right lateral confluent.

(i) *Median Lobe Confluent with Right Lateral Lobe.*—As shown in Fig. i', the pictures obtained are the counterpart of h'.

(j) *Median Bar Confluent with Both Lateral Lobes.*—In such a case we have only one cleft and that in A, the median bar being continuous with the lateral lobes without intervening clefts, as shown in Fig. j'.

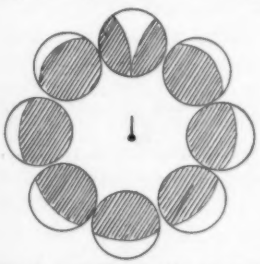

FIG. j'.—Median confluent with both lateral lobes.

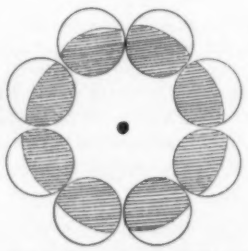

FIG. k'.—Collarette without clefts.

(k) *The Collarette. All portions being enlarged and continuous without intervening clefts.*—In these cases the prostate projects into the bladder in the shape of a collar, the median bar and the lateral lobes all being continuous with each other without definite intervening sulci. In such cases the cystoscopic pictures show a continuous enlargement all round the prostatic orifice, as shown in Fig. k'. The extent of the enlargement cannot be shown in the pictures, which do not appear to differ greatly from those of the normal, but this must be determined by the relations of adjacent parts (ureters, bladder wall, etc.).

(l) *Large Median Lobes.*—In Fig. c we saw the inverted crescent shaped orifice produced by a median lobe. If the urethra in such a case be opened anteriorly, we find it divided at a point in front of the median lobe into two ditches, one of which passes on each side of the median lobe—the Y-shaped urethra of Thompson. If the lobe is small, or if it springs from a base well in the bladder (an hypertrophy of the subcervical group of glands beneath the anterior portion of the trigone), the orifice may be very little enlarged, and the shaft of the cystoscope will be found in the median line resting against the anterior surface and summit of the lobe. The cystoscopic pictures in such a case were given in Fig. c'.

If, however, the orifice of the urethra is widely separated by a prominent, anteriorly directed median lobe, the cystoscope will generally pass into the bladder along one of the branches of the Y and the shaft will be found to occupy "by choice" the sulcus to one side of the lobe, as shown in Fig. 9.

It is an easy matter, as a rule, to carry the cystoscope into the other sulcus by successively depressing the outer end of the instrument, pushing it in the opposite direction, and then elevating it. This manœuvre will generally cause the vesical end of the cystoscope to traverse the front of the middle lobe from one sulcus to the other. If the middle lobe is quite high it is advisable to hug the anterior vesical wall with the beak of the cystoscope rotating the shaft, as the manœuvre described

Fig. 9.—A position "of choice" in large middle lobe hypertrophy. Cystoscope in one of the sulci.

above proceeds, so as to keep the beak continually directed away from the middle lobe.

These manœuvres were made use of by the writer in performing the Bottini operation in middle lobe cases, and were fully described in "Monatsberichte für Urologie," January, 1901. The cautery incisions were by this technique directed across the base of the middle lobe, thus dividing the greater part of its blood supply and leading to atrophy.

If in a case of marked median lobe hypertrophy the cystoscope lies in the sulcus to the right of the lobe, we will see, when looking to the left, not the left lateral lobe, but the right side of the median lobe. The cystoscopic pictures taken from this position are shown in Fig. l'. These were taken from a case with large median lobe hypertrophy. As seen here R, RA and RP show that the right lateral lobe is not at all intravesically enlarged. There is no sulcus or cleft shown in RP, because the cystoscope lies at the bottom of the cleft flattening it out so that we see only the mucous membrane connecting the two lobes. In P we begin to see the base of the median lobe, and rotating the instrument further to the left we see the increasing prominence of the median lobe in LP and L. In LA its summit appears and in A we see the cleft which separates it from the anterior border of the prostatic orifice. We notice here also that the mucous membrane

is not continuous from one to the other, as is the case with sulci which separate the median lobe from the two lateral lobes posteriorly as seen in Fig. c', because the middle lobe is necessarily separated from the anterior border of the prostatic orifice by the urethra.

After preparing the above set of pictures we placed the cystoscope in the bottom of the sulcus to the left side of the middle lobe by the manœuvre described above (*viz.:* beak to right, (R) cystoscope drawn out till beak hugged right lateral edge of the prostatic orifice, handle of the instrument depressed, and carried slowly to the right, beak at same time being rotated through RA, A, LA, L. Handle elevated when the beak reached LP, thus placing the instrument in the left sulcus, having traversed the crescent in front of the middle lobe).

The pictures obtained from this position are shown in Fig. l''. We see at once that they are the counterpart of those of l', taken from the opposite sulcus. The left lateral lobe (shown in L and LA) is seen to be a little larger than the right lateral, and the bottom of the sulcus (LP) is not absolutely obliterated. The non-continuity of the median lobe and the anterior portion of the prostatic orifice is shown in A. The

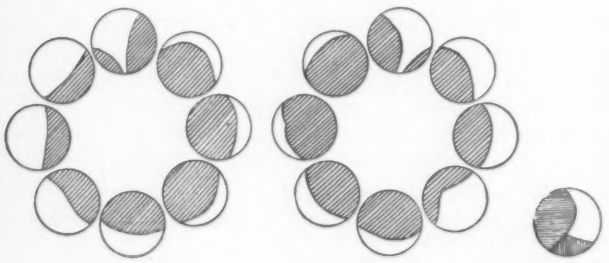

FIG. l'. FIG. l''. FIG. l'''.

FIG. l'.—Large median lobe. Pictures from right sulcus.

FIG. l''.—Large median. Pictures from left sulcus.

FIG. l'''.—Normal anterior segment of urethral orifice behind middle lobe.

median lobe is shown to be more rounded and prominent on this side (P, RP, R, RA and A).[1]

In some instances picture A does not show a cleft absolutely open, but thus, Fig. l'''. Further examination will show, however, that the left side of the cleft is at a higher (or more distant) level and by elevating the cystoscope it is possible to follow this border of the prostatic orifice until the middle lobe disappears from view (the cystoscopic shaft intervening). By continuing the process (rotating the shaft, etc., in reverse order of the manœuvre described before), the instrument will be carried across into the other sulcus and to the right of the lobe.

In many cases it is possible to get three sets of pictures from a middle lobe case. One from the top of the middle lobe, as in Fig. c', and one from each lateral sulcus, as in Figs. l' and l''.

[1] The cystoscopic diagnosis was confirmed in this case by the suprapubic removal of a moderately large median lobe.

Changes in size and shape vary with the position of the cystoscope.—In a normal case, if the handle of the cystoscope is greatly depressed with the beak looking downward, the interureteral bar may appear almost on a line with the edge of the median portion of the prostate, as shown in 1, Fig. m. If the handle be gradually elevated, the distance between the two will be correspondingly increased, as shown in 1, 2, 3, 4 (the latter being the position in which the handle is elevated above the horizontal).

In the same way the ureteral orifices may be made to disappear behind the prostatic orifice by depression of the handle of the cystoscope, as in 1, Fig. n, in which the beak is directed toward the right ureter. By elevating the handle the distance between the two is progressively increased as shown in 2, 3 and 4.

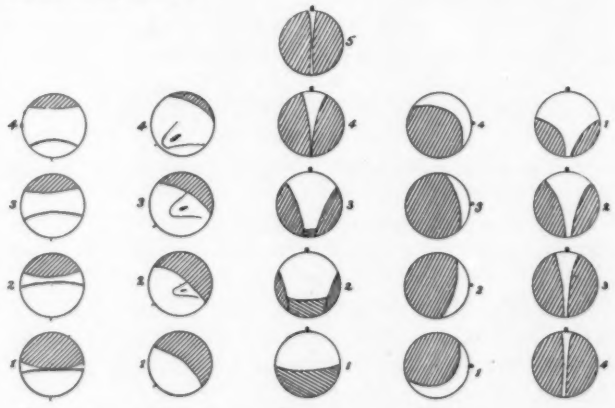

FIG. m. FIG. n. FIG. o. FIG. p. FIG. q.

FIG. m.—Changes in distance between median bar and interureteral bar by elevating handle of cystoscope.

FIG. n.—Ditto for ureteral orifice.

FIG. o.—Different views of an anterior cleft as seen by progressively elevating handle of cystoscope.

FIG. p.—Large left lateral lobe as seen by elevating handle.

FIG. q.—Views obtained by simply drawing cystoscope out.

FIG. 10.—Showing difficulty of seeing ureters and interureteral bar when an enlarged median bar is present.

Such a series of observations is often of great value in determining the height of a median bar. If you are unable, as shown in Fig. 10, even with considerable elevation of the handle of the cystoscope, to see the ureteral orifices or the ligamentum interutericum, you know at once that the ureters lie beneath a fairly large median bar. If, however, they can be brought into plain view, well above the prostatic median portion, the median bar is slight. The same rule holds good for median lobes, when the cystoscope remains on top of the enlargement. If the shaft of the instrument slips to one side of the lobe (into one of the sulci), the orifices are often brought clearly into view, although the lobe is large.

Likewise the picture presented by a cleft between two lobes varies greatly according to the position of the cystoscope, as shown in Fig. o, in which the beak is directed upward between two enlarged lateral lobes. When the handle of the instrument is greatly depressed, the inner end of the shaft is pressed up into the upper limit of the sulcus, the lobes are widely separated and the cleft is flattened out. The prism of the instrument then shows only the tautly-stretched transverse fold of mucous membrane which runs across from one lobe to the other, as seen in 1. As the handle of the cystoscope is gradually elevated the prismatic end descends, and the lateral lobes begin to appear on each side (2 and 3), the transverse fold of mucous membrane disappears from view (4), and finally we see only the narrow chink which separates the closely approximated lobes (5).

This series of pictures is of great value in showing the extent of the hypertrophy, and the depth of the ureteral cleft. In the case from which these pictures were copied the lateral lobes were very large and extended far into the bladder (as shown by prostatectomy). In other cases where the lateral lobes are less prominent the cleft is shallower and does not appear as the narrow chink shown above in 5.

If, while the prism of the cystoscope is directed toward one of the enlarged lateral lobes, the shaft be raised or lowered, different portions of the lobe will be seen and the picture correspondingly changed, as shown in Fig. p (taken from the case referred to above). Here the beak is directed toward the left lateral lobe. In picture 1 the handle is much depressed and we see the upper or anterior curved border of the lobe, in 2 and 3 it has been gradually elevated and the middle portion is shown, in 4 the handle is greatly elevated and we see the lower edge of the intravesical projection of the lobe. In this series of pictures we have transversed the entire intravesical curvature of the lobe parallel to the plane of the urethra.

If again, while holding the shaft and beak in a relatively fixed position, the instrument be gradually drawn outward, the pictures progressively change in certain cases, *e. g.*, with the beak looking up between the enlarged lateral lobes at a point where their intravesical summits approach each other, the picture obtained is shown in 1, Fig. q. The instrument was then gradually drawn out, without elevating or depressing the shaft, and the pictures shown in 2, 3 and 4 obtained, which, interpreted, simply means the lobes approach closer and closer to each other as you come outward.

Remark.—I have given thus in detail the multitudinous changes of view which may be obtained in certain cases of hypertrophied prostate in the hope that many of the pictures which seem hopelessly inexplicable may be brought to a simple interpretation by due consideration of the laws governing the cystoscopy of the prostate. I will now give a few illustrated cases, in which it will be noticed that I have made routine use of a square of circles surrounding the ordinary circular prostatic set. I have found these very valuable in recording not only the changes of view brought about by change of position of the cystoscope, but also the presence of other interesting concomitants; diverticula, tumors, stones; changes in the ureteral orifices, in fact anything which may be pictorially recorded. The point indicates always the direction of the beak of the cystoscope, and where a series is taken with the beak in one direction, the lowest picture corresponds to the lowest position of the handle; the farthest to the right or left the corresponding direction of the handle, and *vice versa*.

CASE I. *Chronic prostatitis, with slight thickening of median portion of prostate. Prostatic massage. Cure.*

K., aged 72, male, complained of great frequency of urination of several years' duration. Examination showed that the prostate by rectum was indurated, but little enlarged, and that the seminal vesicles were indurated. The secretion obtained by massage of the prostate showed many pus cells. There was no stricture present, the catheter passed easily, and there was no residual urine found. The cystoscopic pictures of the prostatic orifice are shown in Fig. 11. There was a slight increase in thickness in the median portion of the prostate (P and LP), but the ureters were easily seen. With the beak looking downward (series D), when the handle was greatly depressed the interureteral bar was not visible, but by elevating the shaft it came into view (2) and continuing the process still more of the trigone

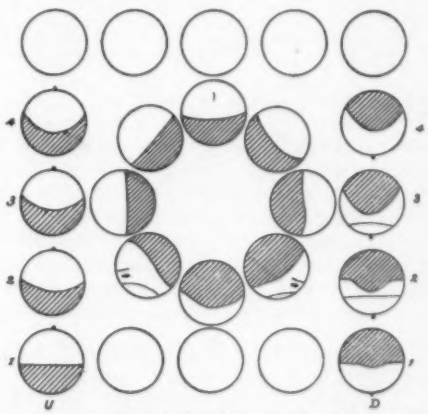

FIG. 11.—Case I. Slight enlargement median portion.

was visible (3 and 4), but the more rounded contour of the posterior surface of the small median bar was seen (4).

With the beak looking upward (series U), the absence of a cleft, when the handle of the cystoscope was gradually elevated, showed that no lateral enlargement was present. (2 and 3). The diagnosis of chronic prostatitis, with slight thickening of median portion of prostate was made, and its correctness verified by cure of the case with prostatic massage.

CASE II. *Enlargement of both lateral lobes, with small posterior fold joining them. Prostatectomy. Cure.*

J. T. Y., aged 60, male, admitted with a suprapubic fistula, the result of an operation six months ago. On rectal examination, both lateral lobes of the prostate were considerably enlarged, and between them at the upper end, the notch was wide and deep. The cystoscope showed considerable enlargement of both lateral lobes which were separated by a deep cleft in front (A and series U), but were joined by a transverse fold of mucous membrane posteriorly. Looking downward (series D), with the handle depressed, the two lateral lobes came together leaving only cleft enough to see the tranverse fold in the median portion (1). On elevating the handle the lobes were pushed aside and only median fold was seen. With the finger in the rectum and the

cystoscope in the urethra the median portion of the prostate showed no increase in thickness. The diagnosis of an intravesical hypertrophy of only the two lateral lobes was made. Another cystoscope inserted into the suprapubic sinus, showed exactly what had been predicted—two enlarged lateral lobes and between them the urethra compressed into a vertical slit (X), and a transverse fold joining the lobes posteriorly in the median portion of the prostate (Y). The other cystoscope in the urethra was seen to lie at the bottom of the cleft (Z).

Nitze's new retrograde cystoscope was then introduced through the urethra and an attempt was made to map out the prostatic enlargements. The vertical slit of the urethra between two lateral lobes was seen when the beak was directed anteriorly. But on looking outward and downward it was absolutely impossible to get any idea as to the size and shape of the lateral lobes. Later the two lateral enlargements were removed by the perineal route, and the absence of median hypertrophy confirmed. The urethra and ejaculatory ducts were preserved, and the patient has had an excellent result.

The necessity of series D is shown in this case, for without it we would have failed to find the posterior cleft, which was not shown in the ordinary "prostatic set" as seen above, P showing a transverse straight line (the transverse fold joining the two

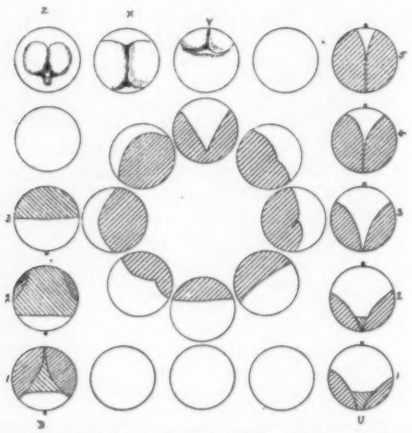

Fig. 12.—Case II. Moderate bilateral hypertrophy.

lobes). As seen with the second cystoscope in Z, the instrument lay at the bottom of the cleft against the transverse fold, separating widely the lateral lobes.

Case III. *Great intravesical enlargement of both lateral lobes. Prostatectomy. Cure.*

W. F. S., male, aged 55 years, leading catheter life. Prostate by rectum greatly enlarged. The cystoscope showed a very great intravesical enlargement of each lateral lobe, the urethra being transformed into a very deep vesical slit, as shown by the deep clefts in A and P. The great depth of those clefts is shown in both U and D. In No. 1, of series U, the handle greatly depressed and we see the curved anterior margin of urethra, the cleft having been flattened out, but in 2 when the handle was slightly elevated the sides of the lateral lobes appear, and as we elevate the handle more and more only a narrow chink remained between. Similar pictures were obtained by looking downward (D): in 1, (the handle being depressed), a median joining fold is seen, but this rapidly disappeared as we elevated the cystoscope.

The median fold was differentiated from a bar also by the fact that the ureters and trigone were plainly visible (X and Y), and because with the finger in the rectum no increase in the median portion of the prostate could be felt between it and the cystoscope.

The patient came to operation—perineal prostatectomy. Both lateral lobes were very large, but there was no enlargement of the median portion. The urethra and ejaculatory ducts were preserved, and the patient now reports sexual powers normal.

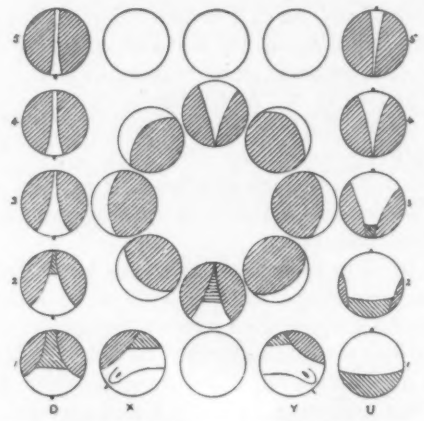

Fig. 13.—Case III. Large bilateral hypertrophy.

Case IV. *Slight prostatic hypertrophy without clefts. Bottini operation. Result shown cystoscopically.*

S. M. J., aged 64 years. Complaint, frequency and difficulty of urination. Onset six months ago with pain.

Examination.—Prostate moderately hypertrophied and slightly indurated. Prostatic secretion contain pus cells. Very little residual urine. Bladder capacity 150 cc.

Cystoscopic examination.—There is a slight enlargement of the lateral lobes and of the median portion of the prostate, but as seen in the pictures (Fig. 14) there are no marked intervening sulci, neither at A between the lateral lobes, nor between and the median in RP or LP. The median bar is therefore continuous

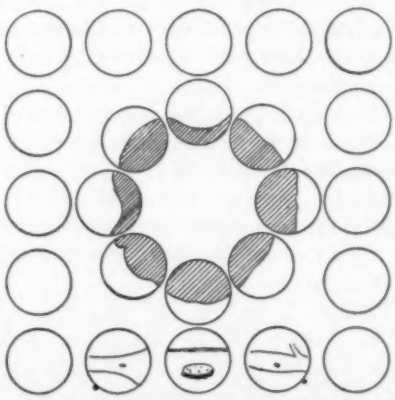

Fig. 14.—Case IV. Slight hypertrophy, median bar and collarette.

with the lateral lobes, but it is slight and the ureteral ridges can be easily seen and are irregularly hypertrophied. Behind the interureteral ridge is a small calculus (see lower circles).

Operation.—Lithotomy. Bottini operation with blade No. 2 (1.2 cm. high) of my instrument; three cuts, one median posterior, one right lateral, one left lateral Result excellent.

Cystoscopy 15 days after operation.—Three sloughs have passed and the lateral cautery incisions are seen in Fig. 15, R

and L, both showing considerable depth and width. The median cut as shown in P is deep, but the edges are closely approximated. There is considerable inflammatory swelling of the mucous membrane of the entire orifice, as seen in all the pictures. In series A No. 1, the handle is pushed far to the right and prism lies in the bottom of the left lateral cut, the ragged edge of which is seen. By carrying the handle to the left the edges of the cut appear in 2, are still closer together in 3, and finally in 4,

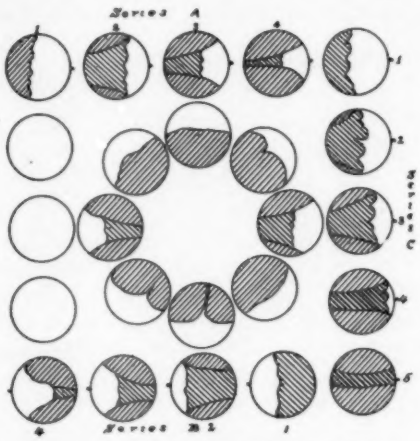

FIG. 15.—Case IV. After Bottini operation.

in which the handle is pushed far to the left, the edges of the cut are seen closely approximated. The same changes, when viewing the other lateral cut from different positions of the prism, are shown in series B. Again in No. 1, the shaft is pushed well into the bottom of the cut, and in the others it is gradually carried away from it allowing the sides to come together. The different views of a cut obtainable by simply drawing the cystoscope out are shown in series C. In 1, the prism is on a level with the

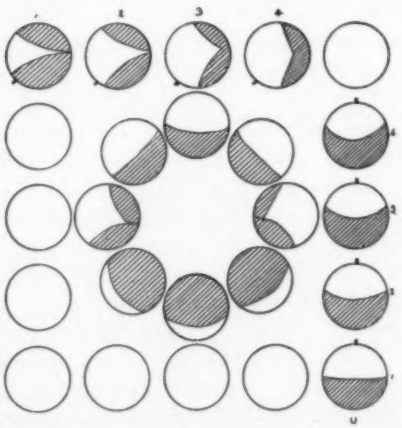

FIG. 16.—Case V. Cystoscope on summit of median lobe.

orifice and lies in the depth of the cut. It is then gradually drawn out, and in 5 when the prism has been drawn far into the urethra only the sides and bottom of the cleft are seen.

These pictures were recorded merely to show how necessary it is to have successive views, especially of clefts, in order to estimate their depth and extent, and to avoid mistakes. If only the No. 1, of the three series had been taken, we would have failed to recognize that a cleft was present.

CASE V. *Small pedunculated median lobe, no lateral enlargement. Perineal prostatectomy. Cure.*

J. R., aged 70, complained of great frequency of urination. The prostate by rectum appeared very little enlarged. Residual urine 460 cc. The cystoscope showed very little intravesical enlargement of the lateral lobes, but a moderately enlarged almost pedunculated median lobe, as shown in the cystoscopic pictures. With the handle of the instrument somewhat depressed the pictures shown in Fig. 16 were obtained. In this the median lobe is shown in P, RP, and LP, and deep clefts on each side in R and

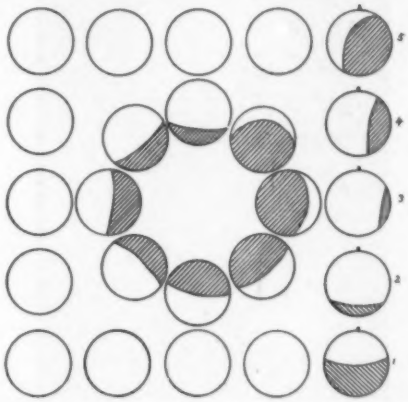

FIG. 17.—Case V. Cystoscope in sulcus to the right of median lobe.

L. Series U with the beak looking upward, the handle being gradually elevated, shows absence of the anterior cleft, which is present if the lateral lobes are hypertrophied. The series of pictures in the top row of circles show the extreme depth of the right cleft in (1), and how it was gradually flattened out by carrying the shaft of the cystoscope into it (2, 3 and 4).

Fig. 17 shows the pictures obtained with the cystoscope in the sulcus to the right of the median lobe, which therefore appears in

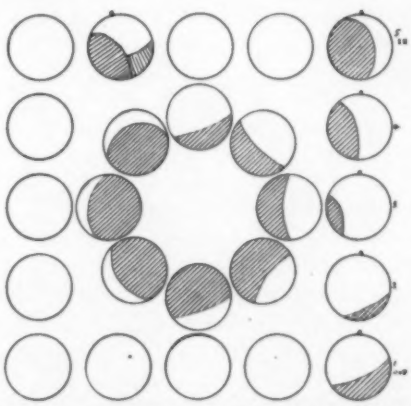

FIG. 18.—Case V. Cystoscope in the sulcus to the left of the median lobe.

L and LA, and the absence of the clefts seen in Fig. 16 in LP and RP. The median lobe does not appear in A, the anterior segment of the urethra alone being seen. By gradually pushing the cystoscope further in as in series U, this anterior segment disappears (after 2) and the side of the middle lobe appears (in 3), and gradually becomes more prominent (4 and 5).

Fig. 18 shows the views obtained with the cystoscope in the sulcus to the left of the middle lobe. They are seen to be the

counterpart of those shown in Fig. 17. In one of the upper line of circles is depicted the summit of the middle lobe obscuring a portion of the anterior segment of the prostatic orifice.

At operation I removed by the perineal route, a small left lateral, a smaller right lateral, and a pedunculated median lobe about 2 cm. in diameter and 3 cm. long, as shown in the accompanying photograph (Fig. 19). The median lobe was enucleated

FIG. 19.—Small lateral lobes and pedunculated middle lobe.

through the left lateral cavity. The prostatic urethra, the ejaculatory ducts, and the bladder were not torn.

This case illustrates well the great magnification of the median lobe obtained in such cases. Had the cystoscope passed first into one of the sulci, one might have easily mistaken the median lobe for an enlarged lateral lobe. However, the series of pictures

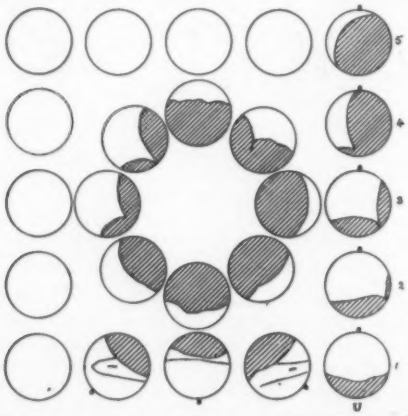

FIG. 20.—Case VI. Large left lateral confluent with median bar and anterior lobe.

obtained by drawing the cystoscope outward while looking steadily upward would have shown at once the lack of continuity of the two lobes. The pictures from other positions (*viz.*, on the top of the middle lobe, Fig. 16), demonstrate clearly the origin of the enlarged lobe.

CASE VI. *Anterior lobe and median bar confluent with large left lateral lobe hypertrophy. Comparatively small right lateral lobe. Perineal prostatectomy.*

S. T. A., aged 70, complained of having had to use catheter for eight years. Rectal examination showed a very considerable enlargement of the prostate. The cystoscopic pictures obtained are shown in Fig. 20. As seen here we found very little intravesical enlargement of the right lateral lobe, a broad median bar confluent with a large left lateral lobe (no cleft between in LP), and an anterior lobe (A) with sulci in RA and LA. The cleft in RA was much deeper, and the pictures obtained by placing the cystoscope into the depths of it (1), and then gradually elevating the handle, are shown in series U. They resemble those obtained

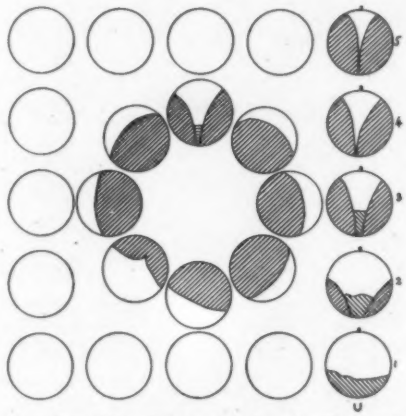

FIG. 21.—Case VII. Bilateral and median bar confluent.

in a case in which a median lobe (posterior) is present, but differ in the important fact that the two lobes are continuous, which is not the case of the median lobe, as remarked above in case V.

Perineal prostatectomy was performed. The right lobe was moderately enlarged weighing g. 28. The median bar, left lateral and anterior lobes were enucleated in one mass which weighed g. 61. The urethra and ejaculatory ducts were preserved. The patient left hospital well.

CASE VII. *Median and bilateral hypertrophy. Prostatectomy. Subsequent cystoscopy.*

W. S. O., aged 58, complained of catheter life. Prostate by rectum moderately enlarged. The cystoscope (see pictures Fig.

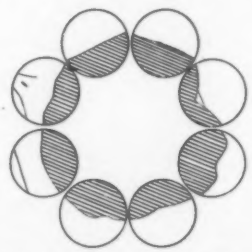

FIG. 22.—Case VIII. After prostatectomy.

21), showed a moderate intravesical hypertrophy of both lateral lobes, and a fairly large median bar which was confluent with the left lateral lobe, but was only separated from the right by a shallow sulcus. The anterior series of pictures (U) showed considerable compression between the lateral lobes when the handle was elevated. The right ureter could be seen behind the bar, but the left could not.

Perineal prostatectomy was performed. The lateral lobes were moderately large, and the median bar was easily enucleated

through the cavity remaining after removal of the left lateral lobe. The urethra and ejaculatory ducts were not disturbed. Cystoscopy performed 10 months after the operation showed an irregular outline, consisting of folds of mucous membrane, but no prostatic hypertrophy as shown in the pictures, Fig. 22. The ureters were easily seen. There is no residual urine present and the patient is cured.

I wish to thank Dr. Halsted and his associates for many courtesies extended.

THE CLINICAL EFFECTS OF SURGICAL ANÆSTHESIA AND OPERATIONS UPON ANÆMIC PATIENTS.

WITH A REPORT OF CASES FROM THE GYNECOLOGICAL CLINIC OF THE JOHNS HOPKINS HOSPITAL.

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Many surgeons regard operations and the giving of a general anæsthetic as contraindicated when the hæmoglobin in the blood is below a certain per cent. Different standards have been adopted by different men. Thus von Mikulicz chooses 30 per cent as his standard; Hamilton Fish advises 50 per cent, and Da Costa and Kalteyer, in a recent article, advocate 40 per cent. These standards have been adopted chiefly as the result of examinations of the blood made during the anæsthetic state. On the other hand, less attention has been paid to the *clinical* effects of anæsthesia and operations upon the very anæmic. The following sixty-one cases have been studied in order to obtain some idea of the clinical effects of operations upon, and the giving of a general anæsthetic to, anæmic patients.

Da Costa and Kalteyer[1] have analyzed the blood during and after fifty anæsthetizations and have concluded that the hæmoglobin is always reduced absolutely and state that, "on account of the hemolysis, a very low percentage of hæmoglobin must be regarded as a contraindication to the administration of a general anæsthetic." They report "one case operated upon with the hæmoglobin 30 per cent and another with 24 per cent," but unfortunately give us no details as to what the operations were or how long the anæsthetic was administered or the effect of the above on the patients.

It has not yet been proved just how general anæsthesia is produced or what part the blood plays in its production, and whether or not the percentage of hæmoglobin can be considered as an important factor in its production. It seems reasonable to suppose that a general anæsthetic would be more injurious to a patient whose blood is low in the oxygen-carrying constituents, than to an individual with a normal percentage of hæmoglobin. As we do not know just how anæsthesia is produced and what part the blood plays in its production, we can, perhaps, best rely on our clinical experience in drawing our conclusions.

An endeavor has been made to collect and review all the cases having a hæmoglobin percentage of fifty or less, which have been operated upon in the gynecological clinic of the Johns Hopkins Hospital. The list is incomplete in many ways: in several of the early cases a definite hæmoglobin percentage was not recorded, only remarks on the "extreme anæmia" having been made; in several cases the hæmoglobin after operation was not carefully followed with the view of noting its increase or decrease; some cases have undoubtedly been overlooked. Satisfactory notes, however, have been made by the anæsthetist, and it is from these notes, together with notes made during convalescence, supplemented by personal observation, that our conclusions have been reached.

HÆMOGLOBIN.

In the articles referred to below, especially those of Bierfreund[2] from von Mikulicz' clinic, of Oliver,[3] and of Da Costa and Kalteyer,[1] especial attention has been paid to the actual reduction in the number of red blood-cells and the lowering of the hæmoglobin per cent during the giving of an anæsthetic. The results obtained are important and the conclusions drawn are of great value. It has been our aim to study, not so much what changes actually take place under anæsthesia as to note the manner in which patients with extremely low hæmoglobin percentages take an anæsthetic and the rapidity and character of their convalescence from operation.

The readings have been taken by the different house officers of the gynecological staff and have been made, for the most part, by means of the von Fleischl instrument, while a few readings have been taken with the instruments of Gowers and of Dare.

Many factors enter into every hæmoglobin estimation; the personal equation of the one taking the reading; the quality of the instrument used; the condition of the part from which the blood is taken; the previous treatment (catharsis, etc.) that the patient has had; and many others. It is partially on account of there being so many conditions influencing all of our hæmoglobin estimations, especially when a patient is under an anæsthetic, that we must look more to the *clinical* evidence of our cases for our help in deciding when to and when not to operate.

The average hæmoglobin percentage of all cases in the following series, taken before operation, is 38.3 per cent. Eight patients were operated upon with a hæmoglobin per cent of *less* than 30, and of these eight, one (No. 39) had 19 per cent and another (No. 54) had 15 per cent. After operation the hæmoglobin was recorded at intervals varying from 6 hours to 9 weeks, as will be seen from the table.

MYOMATA.

No.	Gyn. No.	Name.	Age.	Diagnosis.	Operation.	Length of Op.	Length of Anæs.	Hgb. Before Op.	Hgb. After Op.	Result.	Remarks.
1	4309	M. R.	36	Myoma uteri.	Hystero-myo., left. Salpingo-oöphorectomy.		?	?	40%-20 ds.	Recovery.	Convalescence slow. Phlegmasia Alba Dolens.
2	5447	M. H.	40	Myoma uteri.	Myomectomy.	12 mins.	50 mins.	Anæmic.	Anæmic.	"	Convalescence rapid.
3	5808	M. J.	53	Myoma uteri.	Hystero-myomectomy.	45 "	1½ hrs.	Marked hydræmia.	?	"	Advanced valvular heart disease. Exacerbation during convalescence.
4	6782	U. J. A.	41	Myoma uteri.	Hystero-myomectomy.	1¼ hrs.	2 hrs.	Very anæmic.	26%-21 ds. 62%-27 "	"	Convalescence slow. No complications.
5	6002	A. G.	34	Sub-mucous myoma.	Morcellement of myoma.	44 mins.	50 mins.	?	24%-9 "	"	R. b. c. 1,700,000, 6 days aft. op. Convalescence rapid.
6	6424	L. R.	48	Myoma uteri.	Hystero-myomectomy.	1¾ hrs.	1½ hrs.	Marked anæmia.		"	Convalescence uninterrupted.
7	7098	M. A L.	44	Profuse, continuous uterine hemorrhages. Sub-mucous myoma. Asthenia.	Hystero-salpingo oöphorectomy.	2 hrs. 20 mins.	2½ "	" "		Died.	Death on operating table from asthenia.
8	7433	A. W.	43	Myoma uteri.	Hystero-myo-salpingo-oöphorectomy.	55 "	1 hr. 40 mins.	48%	55%-1 mo.	Recovery.	No complications.
9	8767	E. P.	44	Myoma uteri.	Pan-hystero-myomectomy.	1 hr. 7 mins.	1½ hrs.	50%	67%-10 ds.	"	
10	8804	M. P.	45	Sloughing myoma.	Curettage, irrigation and packing.	5 "	20 mins.	20%	?	Death in 8 hrs.	Enlarged heart. Systolic murmur heard over entire cardiac area.
11	8934	L. P.	40	Sub-mucous myoma.	Pan-hystero-myomectomy.	1 hr. 25 mins.	1 hr. 55 mins.	33%	?	Recovery.	No complications. Went home in good condition.
12	8951	E. M.	48	Myomata uteri.	Hysterectomy, vaginal.	55 "	47 "	37%	?	"	
13	9053	H. W.	43	Myomata uteri.	Pan-hystero-myomectomy, abd.	?	1 hr. 20 mins.	35%	47%-3 wks.	"	Convalescence rapid. No complications.
14	9203	S. B.	36	Interstitial and sub-mucous myomata. Polypoid endomet.	Hystero-myomectomy, abd.	1 hr.	1 hr. 35 mins.	46%	75%-1 mo.	"	Condition excellent.
15	9291	U. P.	50	Myoma uteri.	Pan-hysterectomy, abd.	1 hr. 7 mins.	1 hr. 35 mins.	22%	36%-3 wks.	"	Rapid convalescence. No complications.
16	9296	M. S.	31	Myoma uteri.	Hystero-myomectomy, abd.	1 hr. 3 mins.	1 hr. 20 mins.	45%	?	"	Ether well taken.
17	9678	N. D.	34	Myoma uteri. Abscess.	Myomectomy. Evacuation of abscess.	35 "	43 "	26%	45%-8 wks.	"	Mitral insufficiency. Chronic interstitial nephritis.
18	9707	A. C.	42	Myoma uteri.	Pan-hystero-myomectomy.	40 "	45 "	Anæmic.	26%-14 ds. 55%-5 wks.	"	Stood operation fairly well.
19	9788	M. B.	40	Myoma uteri. Tubo-ovarian abscess.	Pan-hystero-myomectomy.	1 hr. 10 mins.	1 hr. 50 mins.	43%	55%-3 "	"	Ether well taken. Rapid convalescence.
20	10172	W. B.	41	Myoma uteri.	Pan-hystero-myomectomy.	45 "	1½ hrs.	44%	40%-3 ds. 53%-3 wks.	"	Convalescence rapid.
21	10872	D.	28	Sub-mucous myoma.	Vaginal myomect.	30 "	?	40%	60%-1 mo.	"	Slow in regaining color.
22	11077	E.	40	Myomata uteri.	Pan-hystero-myomect., abd.	35 "	1 hr.	22%	25%-9 ds. 29%-12 " 80%-35 "	"	Anæsthetic very well taken. Slight nausea following.
23	11139	J.	43	Myomata uteri. Sub-mucous, profuse hæmorrhage.	Pan-hystero-myomect., abd.	30 "	45 mins.	28%	29%-6 hrs. 40%-20 ds.	"	Anæsthetic well taken. Considerable loss of blood. Not infused or stimulated. Returned to ward warm and in good condition, pulse 104.

CARCINOMA.

24	2248	S. L.	38	Carc. cervix uteri.	Pan-hysterectomy, abd.	2 hrs.	2 hrs. 45 mins.	Very anæmic.	?	Recovery.	
25	5443	W. J. T.	36	Carc. cervix uteri.	Pan-hysterectomy, abd.	35 mins.	1 hr. 15 mins.	Extreme anæmia.	?	Death under anæsthesia.	Basal and apical systolic murmurs.
26	9008	V. K.	44	Carc. cervix uteri.	Pan-hysterectomy. Double implantation of ureters into bladder.	3 hrs. 10 mins.	3 hrs. 6 mins.	45%	?	Recovery.	Returned to ward in good condition. Ether well taken. Convalescence rapid and uninterrupted.
27	10627	F. B.	39	Carc. cervix uteri.	Pan-hysterect., abd.	3 hrs. 16 mins.	3 hrs. 35 mins.	45%	?	"	Left hospital feeling perfectly well.
28	10677	M. P.	40	Carc. cervix uteri.	Pan-hysterect., abd.	1 hr. 30 mins.	1 hr. 35 mins.	45%	?	Unimproved.	Rapid pulse following operation.
29	7819	B.	40	Carc. cervix uteri.	Pan-hysterect., abd.	2 hrs. 25 min.	3 hrs. 8 mins.	35%	?	Recovery.	Profound shock but normal convalescence. Well 4 mos. aft. op.
30	9004	M. W.	49	Carc. cervix uteri.	Hysterectomy, vaginal.	1 hr. 14 mins.	1 hr. 45 mins.	33%	30%-1 mo.	"	Discharged well. Prognosis excellent.
31	7840	L. H.	44	Carc. cervix uteri.	Hysterectomy, vaginal.	1 hr. 50 mins.	2 hrs. 45 mins.	38%	?	"	Anæsthetic well taken.
32	7454	H.	49	Carc. cervix uteri.	Ether exam. and curettage.	3 "	1 hr. 7 mins.	35%	42%-3 wks.		Diagnosis confirmed. Op. followed in 3 wks.
33	7495	H.	49	Carc. cervix uteri.	Vaginal hysterectomy.	1 hr.	2 hrs.	42%	55%-3 "	Recovery.	Rapid convalescence.
34	6581	A. C.	56	Adeno-carc. body and cervix.	Pan-hysterectomy, abd.	1 hr. 20 mins.	2 hrs.	Very anæmic.	?	"	No complications.

CARCINOMA.—*Continued.*

No.	Gyn. No.	Name.	Age.	Diagnosis.	Operation.	Length of Op.	Length of Anæs.	Hgb. Before Op.	Hgb. After Op.	Result.	Remarks.
35	9911	G.	53	Carc. body, cervix and vagina.	Curettage.	25 mins.	40 mins.	35%	58%-2 wks.	Recovery.	Ether well taken.
36	10462	S.	51	Carc. body, uterus. Myoma uteri.	Pan-hysterectomy, abd.	1 hr.	1 hr. 10 mins.	50%	?	"	Ether well taken. Uneventful convalescence.
37	9570	M. H.	48	Carc. body, uterus. Strangulated ovarian cyst.	Pan-hysterectomy, abd.	?	1 hr. 40 mins.	38%	73%-1 mo.	"	
38	9431	M. T.	56	Carc. cervix uteri.	Excision carcinomatous mass.	30 mins.	?	46%	?	Improved.	Recovery from oper. uneventful.
39	7564	W.	50	Carc. cervix uteri.	Curettage.	15 "	55 mins.	19%	37%-1 wk. 44%-3 wks. 59%-5 "	Diagnosis made.	Hysterectomy 6 wks. aft. curettage. Recovery.
40	9387	M.	46	Carc. cervix uteri.	Curettage.	10 "	30 "	35%	54%-2 "	Recovery.	Ether well taken.
41	10130	K.	47	Carc. cervix uteri.	Curettage.	5 "	35 "	50%	?	Unimproved.	Ether well taken.
42	10196	C.	33	Carc. cervix uteri.	Curettage.	20 "	47 "	45%	?	"	Ether well taken.
43	8898	M. D.	67	Carc. bladder.	Resection anterior vaginal wall.	30 "	1 hr. 20 mins.	35%	56%-1 mo.	Recovery.	Convalescence prolonged on account of anæmia.
44	9257	K. E.	20	Carc. ovaries with general mesenteric and omental metastases.	Exploratory laparotomy.	35 "	37 "	43%	?	Recovery (immediate).	Rapid pulse following operation.

POLYPOID ENDOMETRITIS.

45	10362	E. W.	44	Polypoid endometrium.	Pan-hysterect., abd.	55 mins.	1 hr. 30 mins.	45%	?	Recovery.	Anæsthetic well taken. No complications.
46	9040	S. D.	50	Polypoid endometrium.	Pan-hysterect., abd.	?	1 hr. 25 mins.	20%	?	"	Good health 8 mos. after.
47	8413	H. M.	44	Polypoid endometrium.	Pan-hysterect., abd.	55 mins.	1 hr. 20 mins.	38%	52%-24 ds.	"	Convalescence uninterrupted.
48	8905	E. K.	52	Polypoid endometrium.	Hysterectomy, vaginal.	1 hr. 10 mins.	1 hr. 40 mins.	44%	?	"	Convalescence uninterrupted.
49	6128	S. H.	53	Polypoid endometrium.	Curettage.	5 "	27 "	?	33%-20 ds.	"	Very anæmic. Rapid convalescence.
50	5511	W. J.	49	Polypoid endometrium. Hæmorrhoids.	Whitehead operation.	20 "	1 hr.	?	?	"	Excessive anæmia. Bleeding for 7 yrs.

EXTRA-UTERINE PREGNANCY.

51	10329	C. J.	25	Extra-uterine preg. Ruptured.	Evacuation of blood clots.	?	?	30%	68%-20 ds.	Recovery.	
52	7782	S. W.	42	Extra-uterine preg. Ruptured.	Removal.	1 hr. 10 mins.	2 hrs. 10 mins.	30%	?	"	
53	6929	N. S.	27	Extra-uterine preg. Ruptured.	Salpingo-oöphorectomy. Suspension of uterus.	1 hr. 10 mins.	1 hr. 35 mins.	40%	35%-8 ds.	"	Persistence of anæmia 1 mo. aft. op.
54	10078	L. McG.	25	Extra-uterine preg. Ruptured.	Right salpingectomy.	?	20 "	15%	10%-3 "	Died 3rd day.	Progressive diminution in hæmoglobin following operation.

MENORRHAGIA.

55	10165	L. E.	38	Menorrhagia. Cause?	Hystero-salpingectomy.	1 hr. 5 mins.	52 mins.	35%	20%-8 ds. 20%-14 " 30%-31 "	Recovery.	Tendency to hæmophilia. Mitral insufficiency.
56	10097	I. E. R.	43	Menorrhagia. Cause?	Curettage.	?	?	25%	39%-2 wks. 50%-5 " 60%-7 " 74%-8 " 81%-9 "	"	Nitrous oxide anæsthesia. Tonic aft. treatment.

MISCELLANEOUS.

57	10171	E. G. W.	48	Renal calculus. Pyonephrosis.	Nephro-lithotomy.	45 mins.	1 hr. 3 mins.	40%	40%-1 mo.	Improved.	Considerable loss of blood in operation.
58	10377	K.	38	Renal calculus. Pyonephrosis.	Nephro-lithotomy.	25 "	35 "	35%	28%-4½ hrs. aft. op. Infused 700 cc. 2 hrs. before reading.		Rapid convalescence.
59	9974	M. McL.	32	Hæmorrhoids, retro-position. Relaxed outlet.	Suspension of uterus. Repair relaxed outlet.	1 hr. 7 mins.	1 hr. 37 mins.	50%	50%-2 wks.	Recovery.	Anæsthetic well taken. Extreme shock following op. Rapid convalescence.
60	10094	M. S.	34	Deciduoma malignum.	Pan-hysterectomy, abd.	48 "	1 hr.	20%	33%-9 ds. 75%-1 mo.	"	Stood op. well.
61	8759	M. T.	32	Retained membrances.	Curettage.	?	No anæsthesia.	?	38%-5 ds. 46%-16 " 53%-24 "	"	Convalescence slow.

Both acute (emergency) cases and chronic cases have been considered and will be discussed more in detail later. A few cases operated upon early in the history of the hospital have not a definite hæmoglobin percentage recorded, but only those have been considered where especial reference to a "marked anæmia" has been made.

The hæmoglobin per cent has been estimated simply in order to have a basis to work on, but the cases have been considered primarily with reference to, (1) the character of the operation, (2) the length of the anæsthesia, (3) the character of the convalescence and (4) the occurrence of post-operative complications.

Treatment Preliminary to Operations.

Several cases in the above series were subjected to a preliminary tonic treatment before operation was attempted, the treatment lasting from ten days to three and one-half months, and consisting in the administration of the usual tonics—Blaud's pills, Fowler's solution, tinct. nux vomica, etc., accompanied by rest in bed, fresh air and careful nursing. The following cases received such treatment:

No.	Gyn. No.							
14	9203	Hæmoglobin	raised	from	15%	to	46%	in 3½ months.
8	7438	"	"	"	19	"	48	" 1 "
17	9678*	"	"	"	23	"	26	" 1¼ "
30	10172	"	"	"	29	"	44	" ¾ "
47	8413	"	"	"	25	"	38	" 10 days.
19	9786	"	"	"	20	"	43	Time not stated.
27	10627	"	45%.	Tonic treatment				10 days produced no change.

*In this case no tonic treatment was given, patient simply put to bed and "watched."

The above cases show in a somewhat striking manner the value of tonic treatment preceding operative procedures, as far as increasing the amount of hæmoglobin in the blood is concerned, although it will also be noted that the convalescence in these cases was none the more rapid or uneventful than was that in many cases operated upon while having a much lower hæmoglobin percentage and having had no preliminary treatment. If, however, it is possible in a comparatively short space of time to raise the hæmoglobin percentage from 20 to 25 points, one would hardly seem justified in not giving the patient this benefit, however sure one might feel of performing a successful operation without preliminary "building up." Emergency cases are, of course, not considered here as in such cases our only method of procedure is immediate operation, whatever may be the hæmoglobin percentage.

It has been suggested that only the lightest preparation be given to anæmic patients before operation, *e. g.*, a mild cathartic or none at all, and only one enema, with the idea of not weakening a patient any more than can be helped. What few "emergency" cases there are in the above series had, of course, no preliminary preparation. The other cases, like those with higher hæmoglobin percentages, received the full routine preparation for operation, viz.: nothing but liquids after 10 a. m. the day preceding operation; Epsom salts ℥i at 12 noon, repeated at 3 p.m.; enema (oil and glycerine), 8 p.m.; enema (soap suds with turpentine and glycerine), 5 a. m., repeated till "clear." In other words, the immediate preparation for operation of our patients has not been varied in these special cases, and they have, practically, received throughout the same treatment that all of our cases receive.

Anæsthesia.

The anæsthetic used has been ether alone or the nitrous-oxide-ether sequence in every case but one, none of the patients having received chloroform. The method of administration has been invariably the commonly-called "open method," that is, a simple blotting-paper cone covered with oiled muslin and cloth, having a small sea sponge in the apex. Anæsthetics have been administered by the house officers in turn, no regular anæsthetist being employed.

The average length of anæsthesia was one hour and ten minutes. The longest anæsthetization was 3 hours and 35 minutes (No. 27, panhysterectomy abd., carcinoma of cervix, hæmoglobin 45 per cent), and the shortest 20 minutes (No. 10, curettage, sloughing myoma, hæmoglobin 20 per cent, and No. 54, salpingectomy, ruptured extra-uterine pregnancy, hæmoglobin 15 per cent).

As will be seen from the above table, the usual remark made by the anæsthetist on the ether chart, which is kept for every operation, is, "Anæsthetic well taken."

In looking over the post-operative notes made on the wards, it is surprising to learn how well these patients with low hæmoglobin percentages recover from their anæsthetic and how seldom the regular routine for patients after operation has had to be varied in these special cases. Neither nausea nor vomiting has been more marked with these patients, and indeed it has, in many, been entirely absent. Saline infusions have in a few of the cases been given on return to the ward, but oftener as a prophylactic measure than for definite indications.

The exact amount of ether used has not been recorded in a sufficient number of cases to allow of its being tabulated. In those cases where especial attention has been paid to this point, it has been noted, as might be expected, that the amount of the anæsthetic required to produce and maintain surgical anæsthesia has been much less in the extremely anæmic than in healthy persons. Indeed, a surprisingly small amount was required in several cases, considering the open method by which the ether was given and the consequent waste. There are so many conditions influencing the amount of an anæsthetic required, beside changes in the blood itself, that it is difficult to draw conclusions on this point. We agree, however, with Hewitt who states in his "Anæsthetics and their Administration,"[4] that "anæmic patients take anæsthetics very well, small quantities being required to secure tranquil anæsthesia." Hamilton Fish[5] has taken the opposite view, namely, that anæmic patients stand operations and also anæsthesia badly. He states that "a so-called physiological dose of an anæsthetic vapor for an individual whose blood shows a hæmoglobin percentage of 80 per cent, would be a pathological dose in the same individual showing a hæmoglobin percentage of 50 per cent or less." It is difficult to speak of "dosage" in regard to an anæsthetic, and a patient with a hæmoglobin

percentage of 50 would not be given the same "dose" as a patient with 80 per cent because he would not require it.

Fish also attributes respiratory failure to a lowering of the hæmoglobin per cent below 20 and cites three cases of von Mikulicz dying of operative collapse, 15 per cent of hæmoglobin being found remaining in the blood. Patients Nos. 15, 22 and 60 were each anæsthetized for at least one hour, the hæmoglobin being 22 per cent in the first two and 20 per cent in the third. There was no respiratory distress or failure in any of these cases, nor was there any in case No. 54, where the anæsthetic was administered for 20 minutes to a patient having a hæmoglobin per cent of 15. Our cases have, on the contrary, been singularly free from respiratory distress.

The administration of an anæsthetic to the anæmic is far from being without its dangers. Here our "working area" between too light anæsthesia and the danger point of too deep an anæsthesia is considerably lessened and the patient must be closely watched. So little of the anæsthetic is, however, usually required, that, unless the operation be unfortunately complicated by hemorrhage, the administration is easy and reasonably safe.

Da Costa and Kalteyer[1] come to the following conclusion in regard to the giving of a general anæsthetic to anæmic individuals: Finding an absolute corpuscular reduction in hæmoglobin in all cases, they state that a general anæsthetic must not be administered, unless under stress of absolute necessity, if the hæmoglobin is below 40 per cent. The limit set by Hamilton Fish is 50 per cent; that set by von Mikulicz, 30 per cent. In the fifty cases in which the blood changes under anæsthesia were studied by Da Costa and Kalteyer, no case has been considered in which the hæmoglobin was below 50 per cent, and only four cases with hæmoglobin below 70 per cent. These cases were studied with reference to the blood changes alone, without especial regard to the behavior of the patient both during and after anæsthesia. These experiments, performed with the utmost care, have apparently demonstrated the actual corpuscular loss of hæmoglobin in most cases, taking the color index of the blood before and after operation as a basis. Many factors, however, as stated by the authors, enter into determinations of this kind and help influence results. Granting that there is an actual corpuscular loss of hæmoglobin under anæsthesia, it is quite justifiable on purely theoretical grounds to have, as a guide, a definite standard of hæmoglobin per cent and to refuse to operate when the blood fails to come up to this standard. With a view of determining how actual this standard is, the present study of cases with hæmoglobin under 50 per cent has been made.

CONVALESCENCE.

The short notes appended to the above table give a general idea of the character of the convalescence. The immediate results of the anæsthetic have been considered under that heading.

There seems to have been little difficulty in producing a movement of the bowels after operation by means of the routine treatment, which consists of calomel grains II to III given the night of the second day after operation (day of operation being counted as the first day), an ounce of Epsom salts the next morning, followed in three hours by an enema.

Post-operative infections have been few. The blood, with low resistance before operation and with possibly a much lower resistance to infection after operation, has taken care of infections well. In only one case, No. 1, was any trouble at all met with. In this case a femoral phlebitis developed, but soon subsided, and the patient got entirely well. That the phlebitis was the result of the anæmia is possible but not probable. There was no breaking down or infection of wounds in clean cases. Incisions healed rapidly and firmly.

As a general rule, the convalescence was rapid and uninterrupted. In a few cases the recovery seemed to be much prolonged and was attributed to the anæmia alone. These cases were Nos. 21, 43, 53 and 1.

In the early cases reported especial attention was not paid to "tonic" after-treatment. In case No. 53 the anæmia persisted after operation in spite of continued attempts to nourish the patient and to raise the hæmoglobin percentage. She got perfectly well, improving slowly after leaving the hospital. In case No. 54 we have what might be called the extreme lower limit of our series. The hæmoglobin never regained its original level at the time of operation (15 per cent), and the patient died on the third day. In this case, which was one of ruptured extra-uterine pregnancy, no operation would have been performed had it not been absolutely necessary. It was strictly an emergency condition.

On the whole the convalescence of our anæmic patients has proven quite satisfactory and much more rapid than one would expect from the conditions present at the time of operation.

CLASSIFICATION.

I. Myomata.

Of myomata there were 23 cases with two deaths.
The cases may be divided as follows:

1.	Myoma requiring	hysterectomy	(abd.)	17	cases.
2.	" "	"	(vag.)	2	"
3.	" "	myomectomy		2	"
4.	" "	curettage		2	"

In the cases in which hysterectomy was performed:

The	average	length of	operation	was	1 hour	3	minutes.
"	"	" "	anæsthesia	"	1 "	30	"
"	longest		"	"	2¼ hours.		
"	lowest	hæmoglobin per	cent	"	22%		
"	highest	"	"	"	50%		
"	average	"	"	"	38%		

In the other six cases:

The	average	length of	operation	was	30	minutes.
"	"	"	anæsthesia	"	42	"
"	longest		"	"	50	"
"	lowest	hæmoglobin per	cent	"	20%	
"	highest	"	"	"	40%	
"	average	"	"	"	30%	

Of these 23 cases all but 2 recovered and were discharged from the hospital well. Both fatal cases were extremely sick patients. Both had submucous myomata, both had bled pro-

fusely, and No. 10 was an infected case having a hæmoglobin per cent of 20 and broken cardiac compensation.

II. Carcinoma.

We have in our series 21 cases of carcinoma, which may be divided as follows:

1.	Carcinoma of cervix of the uterus	15
2.	" " " and body	2
3.	" " body of the uterus	2
4.	" " ovaries	1
5.	" " bladder	1

1. Carcinoma of cervix.
   (a) In 9 cases hysterectomy was performed.
   (b) In 6 cases curettage.

(a) In the 9 cases in which hysterectomy was performed:

The average length of operation	was 1 hour 53 minutes.
" " " " anæsthesia	" 2 hours 28 "
" longest anæsthetization	" 3 " 35 "
" average hæmoglobin per cent	" 40%
" lowest " "	" 33%
" highest " "	" 45%

(b) In the 6 cases in which curettage only was done:

The average length of operation	was 13 minutes.
" " " " anæsthesia	" 46 "
" longest anæsthetization	" 1 hour 7 minutes.
" average hæmoglobin per cent	" 38%
" lowest " "	" 19%
" highest " "	" 50%

Of these 15 cases, all but one (No. 25) recovered from operation and were discharged from the hospital. In the one fatal case, in which the hæmoglobin per cent was not taken, "extreme anæmia" was present. The patient had both basal and apical heart murmurs and died on the table after ether had been administered for 1 hour and 15 minutes.

2. In the remaining 6 carcinoma cases:

The average length of operation	was 50 minutes.
" " " " anæsthesia	" 1 hour 14 minutes.
" longest "	" 2 hours.
" lowest hæmoglobin per cent	" 35%
" highest " "	" 50%
" average " "	" 40%

All of these six cases recovered from the operation well, although in two cases no permanent benefit could be given on account of the extent of the growth.

III. Polypoid Endometritis.

There were 6 cases with no deaths. In 4 cases hysterectomy was performed. In 2 cases dilatation and curettement. In the 4 cases where hysterectomy was performed,

The average length of operation	was 1 hour.
" " " " anæsthesia	" 1 hour 29 minutes.
" longest "	" 1 " 40 "
" lowest hæmoglobin per cent	" 29%
" highest " "	" 45%
" average " "	" 39%

The two cases, Nos. 45 and 46, may well be compared as regards length of anæsthesia and operation and character of convalescence, while on the other hand one patient showed a hæmoglobin per cent of only 29, but the other 45 per cent. Both patients were over 40 years of age.

IV. Extra-Uterine Pregnancy.

There were 4 cases with one death.

The average length of operation	was 1 hour 10 minutes.
" " " " anæsthesia	" 1 " 22 "
" longest "	" 2 hours 10 "
" lowest hæmoglobin per cent	" 15%
" highest " "	" 40%
" average " "	" 31%

All the cases had ruptured, blood being present in the abdominal cavity. Case No. 52 is remarkable for the length of time (2 hours and 10 minutes) during which the patient received the anæsthetic while having a hæmoglobin per cent of only 30. The anæsthetic was well taken and the patient made a rapid and uneventful recovery.

The fatal result in case No. 54 was expected even sooner than it occurred. The taking of the anæsthetic for twenty minutes seemed to have but little effect one way or the other, on the general condition.

V. Menorrhagia. (Cause not stated.)

2 cases.	No deaths.
Average Hgb.	30%
Lowest	25%
Highest	35%

Case No. 55 proved an interesting one. The operation consisted in the removal of the uterus and both tubes and lasted for 1 hour and 5 minutes, the anæsthesia lasting 52 minutes. Complications were, (1) mitral insufficiency, and (2) a distinct tendency to hæmophilia, which in itself might be considered a contraindication to any prolonged operation. There was a decided diminution in the hæmoglobin percentage following the operation, it reaching only 30 per cent 31 days after the operation. Even under these adverse conditions the patient stood the anæsthetic well and was sent home at the end of one month much improved generally.

Case No. 56 was the only one in the series where ether was not used, the patient being given here only the nitrous oxide gas—hgb. 25 per cent. The patient was 43 years old. The rapid increase in hæmoglobin following operation is shown in the above table.

Case No. 61 is included in the series for the purpose of comparison. Hæmoglobin per cent before operation was not stated. No anæsthesia was given to the patient. A simple curettage was performed for bleeding from retained membranes. It is noted in the history that the convalescence in this case was "slow," although there was a satisfactory increase in the hæmoglobin following the operation. From a comparison with other cases it would seem as though an anæsthetic might have been safely given to this patient also, had one been needed for a more thorough examination or operation.

We have left cases Nos. 57, 58 and 60. No. 60 was especially satisfactory, as here a radical abdominal operation was demanded from the nature of the case (deciduoma malignum) and was performed, although the hæmoglobin registered only

20 per cent. The anæsthetic was administered for one hour. The patient stood the operation and the anæsthesia "well" and made a rapid and very satisfactory recovery.

Patient No. 58 was desperately ill—an emergency case (nephrolithiasis with pyonephrosis). Patient looked extremely anæmic, although the hæmoglobin proved to be 35 per cent. Recovery from operation rapid. The kidney was removed later when the hæmoglobin had reached 67 per cent.

RESULTS.

Sixty women, each showing a hæmoglobin percentage of 50 or less, have received a general anæsthetic for operative purposes, the duration of the anæsthesia varying from twenty minutes to three and one-half hours.

Fifty-six of the sixty cases had uneventful recoveries. There were four fatalities, Nos. 7, 10, 25 and 54. Severe heart lesions complicated two of these; in the third, the patient had already bled till her hæmoglobin registered 15 per cent, and in the fourth case the anæsthetic had been given for two and one-half hours before the patient showed any signs of immediate collapse.

Two cases only died on the table under the anæsthetic.

The worst shocked patient of all was No. 59, upon whom, with a hæmoglobin percentage of 50, an ordinary suspension of the uterus and repair of relaxed vaginal outlet were performed, the operations consuming an hour and seven minutes.

The patients, as a rule, have taken the anæsthetic well. There has been no respiratory distress noted, and in neither of the cases dying on the table was respiratory failure primarily the cause of death.

Recovery from the anæsthetic and the following convalescence has been satisfactory in a great majority of the cases. In no case was it thought that the persistence of the anæmia after operation was in any way prolonged by the giving of the anæsthetic.

Preliminary tonic treatment proved of value in raising the hæmoglobin percentage in the six cases in which it was tried.

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2. Hamilton Fish: The Importance of Blood Examinations in Reference to General Anæsthetization and Operative Procedures. Annals of Surgery, 1899, XXX, 79-90.

3. Max Bierfreund: Ueber den Hämoglobingehalt bei chirurgischen Erkrankungen, mit besonderer Rücksicht auf den Wiederersatz von Blutverlusten. Archiv für Klinische Chirurgie, 1890, 1-63.

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5. Bloodgood: The Importance of Blood Examinations in Reference to General Anæsthesia and Operative Procedures. Progressive Medicine, 1900, Dec., 100-102.

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A CONTRIBUTION TO THE STUDY OF CYSTINURIA.*

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HISTORICAL SURVEY.

While the sulphur and nitrogen content of cystin had long been recognized as evidence of the albuminous origin of the substance, either directly or indirectly, nothing practically was known of the manner of its formation and its rôle in the sulphur metabolism of the body until a comparatively recent date.

The first important papers in which the subject was approached from the experimental side were published in 1881 by Baumann and Preusse[1] and Jaffe.[2] It was shown that on feeding normal dogs with halogen substitution products of benzol, the aromatic radicles C_6H_4Br—, C_6H_4Cl—, etc., combine with an organic sulphur body to form compounds which are termed mercapturic acids. These in turn appear in the urine in combination with glucuronic acid. According to the character of the aromatic radicle we speak of a bromphenyl mercapturic acid, a chlorphenyl mercapturic acid, etc. Further study of these bodies showed that on hydrolysis they are decomposed into acetic acid and a substance which, in the case of brombenzol, has the composition $C_9H_{10}Br\ SNO_2$. This was identified as bromphenyl-cysteïn, viz., as cysteïn in which one hydrogen atom had been replaced by the univalent C_6H_4Br— group. Providing that this cysteïn could be shown to be identical with the cysteïn which results on reduction of the common cystin found in the urine of cystinuric individ-

* Read in abstract before the Hospital Med. Soc'y., May 2, 1904.

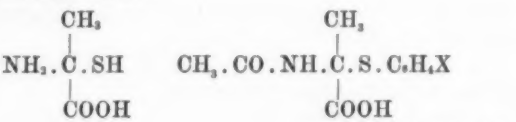
[1] Baumann and Preusse: Zur Kenntniss der synthetischen Prozesse im Thierkörper. Zeit. f. phys. Chem., 1881, vol. XV, p. 309.

[2] Jaffe: Ber. d. deutsch. Chem. Ges., vol. XII, p. 1092.

uals, there would thus be evidence to show that cysteïn, viz., cystin, represents a normal product of the sulphur metabolism of the body.

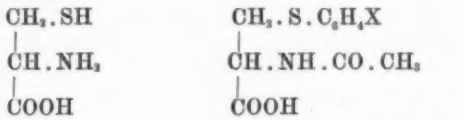
Within recent years this has been definitely established, and the formation of mercapturic acids in the body of the dog can accordingly be regarded as an experimental cystinuria, as Baumann first suggested. Baumann's views regarding the structure of the mercapturic acids and of cystin have undergone a certain modification, however, for Friedmann[3] has shown that the thio-group of cysteïn occupies the β-position and the amido group the α-position, and that Baumann's mercapturic acids have a corresponding structure.[4] The difference from Baumann's original conception is expressed in the formulæ:

Baumann's formulæ:



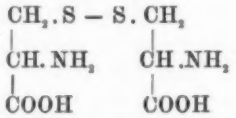
Cysteïn — Mercapturic acid

Friedmann's formulæ:



Cysteïn — Mercapturic acid

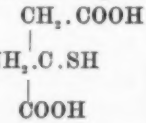
The cystin formula is accordingly:



i. e., it is α-diamido-β-dithio-dilactic acid.

The correctness of Friedmann's deductions has been corroborated by the synthetic formation of the substance by Erlenmeyer.[5]

Regarding the mother substance of cystin, Baumann assumed the existence in the albuminous molecule of a sulpho-asparaginic acid group, of the composition:



This supposition was largely based on Suter's[6] inability to demonstrate cystin among the hydrolytic decomposition products of keratin. Later researches by Mörner[7] and Embden,[8] however, have shown that cystin is a constant decomposition product of the keratins, not only, but of nearly all the common albumins also, and that there is good reason for assuming that the greater portion, if not all, of the sulphur exists in the albuminous molecule in the form of a cystin, or a cysteïn complex. Patten[9] then has shown that cystin is the primary form in which the substance is liberated on hydrolysis, and that cysteïn whenever present has resulted from the cystin secondarily. This albuminous cystin, as it may be termed, is in all respects identical with the cystin obtained from the urine of cystinuric individuals, and the corresponding cysteïn with that which forms the sulphur nucleus of the mercapturic acids.

In the light of these investigations there can be no doubt that cystin represents a normal intermediate product in the sulphur metabolism of the body, and that its occurrence in the urine of cystinuric individuals can scarcely be the expression of a deviation from the normal katabolism so far as its primary formation is concerned. As the substance is not found in the urine under normal conditions, however, we can infer that following its primary formation it is eliminated in altered form, while this does not occur, or does so at least to a less extent in the cystinuric individual.

The first systematic investigations which were undertaken with the object of studying the fate of cystin in the animal body were made by Goldmann.[10] He could show that it is possible in dogs to thus increase the output of non-oxidized sulphur of the urine by feeding with chlorbenzol that the ratio of the non-oxidized to the oxidized form, which in dogs is normally 0.38 : 1 (average of seven analyses), can rise to 3.1. The conclusion thus appeared quite justifiable that normally the cystin, viz., cysteïn, is for the most part oxidized to sulphuric acid, and that it accordingly represents an antecedent of the urinary sulphates. This was further confirmed by an experiment in which a dog was fed 2.02 grms. of cysteïn. The oxidized sulphur, which had been 0.3576 grm. the day before, rose to 0.80 and the non-oxidized sulphur from 0.0984 to 0.26. The ratio between the two remained constant. Two-thirds of the ingested cysteïn-sulphur were thus eliminated in completely oxidized form, while one-third went to increase the non-oxidized sulphur. So far as this second portion is concerned, Goldmann could show that the cysteïn was not eliminated as such, as on boiling the urine with caustic alkali and lead acetate no separation of lead sulphide occurred; that a transformation into sulphocyanides had not taken place could likewise be demonstrated. Noteworthy also is the observation that the non-oxidized sulphur bodies of the dog's urine (even normally) were not destroyed as a result of putrefactive changes. A small amount of hydrogen sulphide is formed, which, however, is derived from the sulphates. Goldmann concludes that the ingested cysteïn underwent the same change as is normally the case with the albuminous sulphur.

The only other feeding experiments with cystin, in which the sulphur elimination of the urine was studied, are those of

[3] Friedmann, E. Hofmeister's Beiträge, 1902, vol. III.
[4] Friedmann, E.: Ibid., 1903, vol. IV.
[5] Erlenmeyer: Ber. d. deutsch. chem. Ges., 1903, vol. XXXVI, p. 2720.
[6] Suter, F.: Zeit. f. phys. Chem., 1895, vol. XX, p. 565.
[7] Mörner, K. A. H.: Zeit. f. phys. Chem., 1899, Vol. XXVIII, p. 595, and 1901-02, and vol. XXXIV, p. 207.
[8] Embden, G.: Ibid., 1901, vol. XXXII, p. 94.
[9] Patten, A. J.: Ibid., 1903, vol. XXXIX, p. 350.
[10] Goldmann, E.: Zeit. f. phys. Chem., 1885, vol. IX, p. 260.

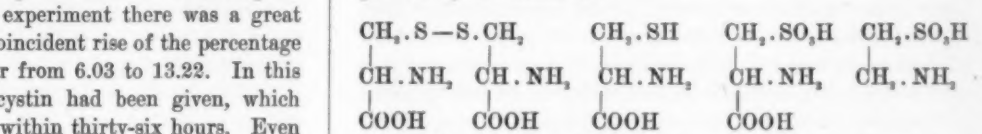
Blum.[11] These were undertaken with the view of testing the hypothesis that cystinuria in the human being might be the result of a more extensive albuminous cleavage than normal, with coincident excessive liberation of cystin. His results show quite conclusively that this view is not tenable. Following the administration of cystin (to dogs) in toxic doses even, cystinuria could not be produced. In these investigations the total non-oxidized sulphur was not determined, but merely that portion from which the sulphur can be split off by boiling with caustic alkali. In one instance it was found that after the administration of 4.5 grms. of cystin there was a marked increase of the oxidized sulphur, while the non-oxidized form was only slightly affected; as a result the percentage amount of the non-oxidized form as compared with the total sulphur was diminished. In a second experiment there was a great increase of both forms, with a coincident rise of the percentage amount of non-oxidized sulphur from 6.03 to 13.22. In this case an excessive amount of cystin had been given, which caused the death of the animal within thirty-six hours. Even here no cystin could be demonstrated in the urine, which shows that in the normal dog at least the organism is capable of so altering any cystin which has been fed by the mouth, that it is no longer demonstrable as such, a considerable portion being oxidized to sulphuric acid. So far as the non-oxidized fraction is concerned, it seems that in the dog a considerable portion can be eliminated in the form of thiosulphates, although this does not occur necessarily, as shown in the first instance, where the non-oxidized sulphur was scarcely increased.

Similar results were obtained by feeding with cysteïn. Cystin could at no time be demonstrated, but the thiosulphates were markedly increased.

In one experiment, in which 1.1 grm. of cystin was given subcutaneously, there followed a corresponding increase of the oxidized, but not of the non-oxidized sulphur.

These experiments thus show that in normal dogs cystin, when introduced in moderate amounts by the mouth or subcutaneously, is largely oxidized to sulphuric acid, while a smaller fraction is eliminated in non-oxidized form, which, however, is not cystin. Its intravenous injection, on the other hand, may give rise to genuine cystinuria. This depends primarily upon the rapidity with which the cystin is introduced and the vein which is selected. Generally speaking cystinuria will result, if the cystin is introduced into a peripheral vein, while this does not occur, if it is made to pass through the liver. Its injection, in this way, unless it is done rapidly and under pressure, increases the oxidized, but scarcely the non-oxidized sulphur. This difference in result which follows the injection of cystin into a peripheral, as compared with a mesenteric vein for example, may be referable to the slowness with which the substance reaches the systemic circulation; but, on the other hand, there is a possibility that the cystin may be changed to taurin in the liver. The possible genetic relationship between the two bodies has been suggested long ago and was urged especially by Marowsky,[12] on the basis of the occurrence of cystinuria in a patient suffering from hepatic cirrhosis with coincident chronic total acholia. Marowsky inferred that in this case the cystin occurred vicariously in place of the taurin.

Notwithstanding the many objections which have been urged against this inference, the case has gained in interest from the fact that the suspected chemical relationship between the two bodies has recently been definitely established by Friedmann.[13] Friedmann succeeded in oxidizing cystin to cysteïnic acid, which may be viewed as the sulpho-acid of cysteïn, and on heating this with water in the sealed tube he obtained taurin. The relationship between these bodies is expressed by the formulæ:



Cystin Cysteïn Cysteïnic acid Taurin

This observation has thrown material light on the possible origin of taurin, of the antecedents of which nothing was formerly known beyond the fact that, like cystin, it was in some manner derived from the albumins. The feeding experiments with cystin, which have been considered above, have shown that a portion of the cystin sulphur, at any rate, is eliminated in the urine. How much of the ingested cystin sulphur is excreted in this manner cannot be determined from the available data; it appears, however, that as a general rule this is quite considerable. Under the circumstances corresponding observations on the sulphur output in the bile promised a great deal of interest. In dogs this is dependent exclusively upon the taurocholic acid, and sulphur estimations in such cases can accordingly be referred directly to taurin. Such experiments have recently been made by v. Bergmann.[14]

The results show the interesting fact that the administration of moderate amounts of cystin (2-2.5 grms.) alone does not lead to an increased elimination of the bile sulphur, but that this occurs if the animal is fed at the same time on cholalic acid. In this manner then the biological proof also has been furnished of the genetic relationship between cystin and taurin.

To sum up, there is evidence to show that under normal conditions the sulphur of the albuminous molecule is set free in the form of cystin, that this is in part eliminated in the bile as taurocholic acid, while another portion is excreted in the urine in completely oxidized form and a small fraction as non-oxidized sulphur, which, however, is no longer cystin. Of the intermediate products which are formed but little is known. In the past it has been tacitly assumed that the formation of taurocholic acid takes place through the direct

[11] Blum, L.: Hofmeister's Beiträge, 1903, vol. V, p. 1.

[12] Marowsky: Deutsch. Arch. f. klin. Med., 1868, vol. IV, p. 449.

[13] Friedmann: Hofmeister's Beiträge, 1902, vol. III, p. 1.

[14] v. Bergmann: Hofmeister's Beiträge, 1903, vol. IV, p. 192.

union of taurin and cholalic acid, analogous to the formation of hippuric acid, as represented by the equation:

$$\begin{matrix} CH_2.SO_2OH \\ | \\ CH_2.NH_2 \\ \text{Taurin} \end{matrix} + C_{20}H_{31}-\begin{matrix} CH.OH \\ (CH_2.OH)_2 \\ COOH \\ \text{Cholalic acid} \end{matrix} = CH_2.NH\,[C_{20}H_{31}.$$

$$CH.OH.(CH_2.OH)_2.CO].CH_2.SO_2OH + H_2O.$$

Taurocholic acid

But, on the other hand, there is evidence to show that the cystin may unite in the liver directly with the cholalic acid and that the resulting compound is then oxidized to taurocholic acid. Blum[15] thus found after injecting 5.6 grms. of cystin into a mesenteric vein of a dog that the liver two hours later contained no taurin; in the bile, however, a substance could be demonstrated from which sulphur could be split off on boiling with caustic alkali, whereas this is not possible under normal conditions, nor, according to v. Bergmann, after feeding dogs with moderate amounts of cystin. Blum could not isolate the body in question, but from his experiments it is clear that the sulphur reaction could not have been referable to cystin in the free state.

Granting the possibility, therefore, that the production of taurocholic acid may occur in this manner, viz.: without the intermediary formation of taurin, it appeared of interest to ascertain in what manner the cystinuric individual would react to the administration of cholalic acid. We were fortunately able to obtain such a case, who consented to act as subject of investigation. As there was a possibility, however, that the sulphur metabolism in man might differ in some respects from the corresponding process in the dog, it was deemed advisable to make control examinations in a non-cystinuric individual, who should receive both cystin and cholalic acid. Mester[16] had shown, as a matter of fact, that in man a recognizable formation of mercapturic acid does not occur following the administration of brombenzol, and Stadthagen[17] found that human urine normally contains no non-oxidized sulphur bodies with the exception of sulphocyanides, from which the sulphur can be split off on boiling with caustic alkali, while in dogs traces of cysteïn are probably normal. We believe that our investigations in this direction, both in the case of the normal as well as the cystinuric individual, are the first which have been undertaken in man.

Personal Studies.

The technical details of our work follow:

Preparation of the Cystin.—The cystin which was used in our experiments was prepared from human hair in the manner described by Friedmann.[18] To this end 500 grm. lots were boiled on the sand-bath with 1500 cc. of concentrated hydrochloric acid (sp. gr. 1.19) for at least four hours. On cooling a concentrated solution of sodium hydrate is slowly added until the reaction is just acid (an alkaline reaction must be avoided). The mixture is then boiled for three-quarters of an hour with animal charcoal, which should be repeatedly added in liberal amounts, and filtered while still hot. On cooling, impure cystin separates out on standing. This is collected on a filter, dissolved in hot 10 per cent ammonia and reprecipitated by adding glacial acetic acid until the reaction is strongly acid. By redissolution and reprecipitation, and if necessary by final spontaneous evaporation of the ammonia, the cystin is ultimately obtained in pure form. Sometimes no separation of cystin occurred from the primary solution on cooling; in that case glacial acetic acid was added, when after twenty-four hours a copious sediment of impure cystin was always obtained, which was then purified as just described. The substance is finally collected on a filter, washed with water, then with alcohol and finally with a small amount of ether. In this manner a product was obtained which was free from tyrosin and in which the crystals presented the characteristic hexagonal form.

Preparation of the Sodium Cholate.—The cholalic acid which was used in our experiments was kindly presented to us by Dr. John J. Abel, of the Johns Hopkins Medical School, to whom we wish to express our indebtedness also at this place. The sodium salt was prepared by dissolving the cholalic acid in as little boiling absolute alcohol as possible, and treating this solution with a corresponding amount of alcoholic sodium hydrate solution (0.0964 NaOH for 1 grm. of cholalic acid). The resulting solution was filtered, while hot, and the filtrate treated with a large excess of ether. On standing the sodium cholate separates out in crystalline form and is filtered off, dried over calcium chloride, and stored for use.

Diet.—The diet in both individuals was constant. Case S. received daily: 250 cc. of milk, 150 grms. of bread, 30 grms. of butter, 4 whole eggs, 175 grms. of lean beef, 30 grms. of rice, 100 grms. of mashed potatoes, 300 cc. of bouillon, 150 cc. of coffee, 200 cc. of tea (both with sugar), and 75 grms. of stewed prunes.

M.'s diet consisted of 325 cc. of milk, 150 grms. of bread, 30 grms. of butter, 4 whole eggs and the whites of two additional eggs, 150 grms. of ham, 175 grms. of lean beef, 30 grms. of rice, 100 grms. of mashed potatoes, 300 cc. of bouillon, 125 cc. of coffee, 200 cc. of tea (both with sugar), and a dish of stewed prunes.

Analytical Methods.—The oxidized sulphur was determined according to Salkowski, and the total sulphur according to Glaser-v. Asbòth, in the modification suggested by Modrakowsky.[19] To this end a couple of grammes of sodium peroxide are placed in a nickel dish and covered with 50 cc. of urine, which is added drop by drop. The fluid is evaporated on the water-bath to a syrup and further treated with 2 or 3 grms. of the peroxide, which is slowly added while stirring. The dish is then removed from the water-bath and heated with a small alcohol flame. If necessary a few more grammes of the

[15] L. c., p. 13.
[16] Mester, B.: Zeit. f. phys. Chem., 1890, vol. XIV, p. 147.
[17] Stadthagen: Ibid., 1885, vol. IX, p. 136.
[18] L. c.
[19] Modrakowsky: Zeit. f. phys. Chem., 1903, vol. XXXVIII, p. 562.

peroxide are added. The mass now forms a brown, oily material and finally becomes thick. This ends the reaction. On cooling the fusion is dissolved in water, and the solution filtered and acidified with hydrochloric acid. Barium chloride is then added and the process continued in the usual manner.

By deducting the oxidized from the total sulphur the non-oxidized or neutral sulphur is obtained. So far as the control case goes, these values were really what we desired. In the cystinuric individual, however, we should have preferred a method by which the cystin could have been estimated as such. Abderhalden[29] has recently recommended a method for this purpose, which is based upon the isolation of the cystin from the urine as a β-naphthalin-sulpho compound, but unfortunately we were not able to procure the necessary reagent at the time when our cystinuric individual was available.

Baumann's benzoylation method is not applicable for the purpose,[30] and the estimation of the loosely combined sulphur and its interpretation as cystin sulphur also did not appear to offer any material advantages over the estimation of the neutral sulphur. Baumann and Goldmann[31] indeed have shown that in cystin urines the yield of sulphide with this method may amount to only 30 per cent of the actual quantity present. For this reason we chose the estimation of the neutral sulphur, well knowing that its amount is subject even normally to not inconsiderable variations. The method seemed quite applicable, however, to decide the main point at issue, and served its purpose very well.

SERIES I.

The subject of the first series of investigations was C. S., male, æt. 43, a case of arthritis deformans. The case was a light one with nothing of interest in his history. There was some stiffness of the back and neck; the right knee was somewhat swollen, but beyond that there were no abnormalities of moment. From our standpoint the individual could be regarded as normal. His diet during the entire course of the study was constant (v. s.). At first his normal sulphur elimination was studied during a period of eleven days; the results of the last five days are given in the following table:

TABLE I.

Date.	Amount of Urine.	Sp. Gr.	Total S, as S.	Oxidized S, as S.	Neutral S, as S.	% of N. S, as compared with total S. (total = 100).
III						
13/14	900 cc.	1.021	0.7304	0.6883	0.0421	7.8%
14/15	1150 cc.	1.017	0.7072	0.6900	0.0172	2.4%
15/16	1120 cc.	1.017	0.7402	0.6598	0.0804	10.8%
16/17	830 cc.	1.020	0.7182	0.6793	0.0389	5.4%
17/18	1070 cc.	1.018	0.7806	0.6265	0.1541	19.7%
Average			0.7353	0.6687	0.0665	9.18%

The figure 9.18 for the neutral sulphur is rather lower than is commonly given. The values obtained by Salkowski,[32] Lepine and Flavard,[33] and Stadthagen[34] vary between 13 and 16.8. The number of analyses which form the bases of these averages, however, are rather small, and it is quite likely that in non-cystinuric individuals even the variations in the excretion of the neutral sulphur are more extensive than is commonly thought. Mester[35] found 18.1 per cent as average of his estimations in nine individuals, the figures varying between 12.3 and 30.6 (!).

The marked variations of the neutral sulphur from day to day are on first consideration rather surprising, but quite analogous to the variations in the bile sulphur, to which Stadelmann[36] already drew attention, and which are also well shown in v. Bergmann's series (0.028-0.062, absolute values). These variations then must be borne in mind in interpreting the results which are observed in feeding studies, such as ours.

On March 18 the individual now received 1 grm. of cystin, corresponding to 0.265 grm. of sulphur; this was administered in divided doses, viz.: 0.25 grm. at 9 and 12 A. M. and 3 and 6 P. M. The daily collection of urine began at 7 A. M. He thus received the entire gramme of cystin within the first twelve hours of the twenty-four. The next day no cystin was given. The day following he received 1.5 grm. of cystin (= 0.397 grm. S.), likewise in divided doses of 0.25 grm. each (at 9 and 11 A. M. and at 1, 3, 5 and 7 P. M.); this was followed by two normal days. The results are shown in Table II, and represent a direct continuation of the series of Table I.

It may be mentioned at this place that the cystin in the doses which we employed (1 and 1.5 grammes) produced no untoward results whatever. That large amounts could not be given with safety was suggested by Blum's experience, whose first dog was found dead within thirty-six hours following the administration of 9.6 grms., death being due to a hemorrhagic nephritis. This dose, considering the weight of the animal, viz., 9 kgrs., was of course excessive. In the second experiment, in which 4.5 grms. were fed to a dog of approximately the same weight, the animal was somewhat languid, but showed no other ill effects.

TABLE II.

Date.	Amount of Urine.	Sp. Gr.	Total S, as S.	Oxidized S, as S.	Neutral S, as S.	% of N. S, as compared with the total S.	Remarks.
18/19	920	1.021	0.6886	0.6038	0.0248	12.2%	1.0 cystu
19/20	1250	1.016	0.8876	0.8204	0.0672	7.8%	
20/21	1000	1.018	0.7771	0.6988	0.0783	10.0%	1.5 cystin
21/22	1480	1.016	1.0146	0.9496	0.0650	6.8%	
22/23	800	1.020	0.6009	0.5911	0.0098	10.5%	

A study of the above figures shows that in the twenty-four hours, during which the one gramme of cystin was given, there was no evidence whatever of an increased sulphur output; the amount of total sulphur indeed was lower than the minimum of the five normal days. Possibly this is in part accounted for by the fact that on the day preceding there was the maximal output of the normal period.

[29] Abderhalden, E.: Zeit. f. phys. Chem., 1903, vol. XXXVIII, p. 559.

[30] Mester: l. c., p. 117.

[31] Baumann and Goldmann: Zeit. f. phys. Chem., 1888, vol. XII, p. 254.

[32] Salkowski: Virchow's Archiv, vol. LVII, p. 501.

[33] Lepine and Flavard: Rev. d. Med., 1881, p. 27.

[34] Stadthagen: Virchow's Arch., vol. C, p. 424.

[35] Mester: Zeit. f. phys. Chem., 1890, vol. XIV, p. 136.

[36] Stadelmann, E.: Der Icterus, Stuttgart, 1891.

The following day values were obtained, which both in the case of the total and oxidized sulphur are well beyond the maximal normal figures. The neutral sulphur at the same time was not increased beyond the average normal. Manifestly the increase is very largely in the oxidized sulphur. As compared with the average normal it amounts to 0.1517 grm. That this plus is referable to the ingested cystin cannot be doubted. Whether or not the increase of the neutral sulphur over the previous day is also due to the cystin is difficult to say, but does not seem improbable. If so, we would have would still be a deficit of 0.17 grm., which can probably only be accounted for by assuming that a portion of this, at any rate, was either retained in the body or eliminated through some other channel. The data obtained on the next day suggest the former possibility as quite likely, for we find that the value of the oxidized sulphur is still somewhat above the maximal normal value, and that the non-oxidized sulphur is even a little higher than on the previous day. On this day cystin had again been given, but as we have seen the elimination of its sulphur apparently does not occur on the same day, and we can accordingly refer the slightly higher value to the first feeding. The following day the oxidized sulphur is very high; 0.397 grms. of cystin sulphur had been given and we find 0.2809 grm. above the average. The balance is not accounted for, as the neutral sulphur was not increased even beyond the previous day, and as on the following day abnormally small sulphur values are found, lower in fact than on any preceding day.

From these analyses we can conclude that under normal conditions in man, as in the dog, the administration of cystin by the mouth leads to an increased elimination of the oxidized sulphur; that by far the greater portion of the ingested sulphur is thus eliminated; that a comparatively insignificant fraction may appear in non-oxidized form, though the evidence in this regard is not conclusive; and that a portion of the cystin sulphur is either retained or eliminated through other channels.

v. Bergmann has shown that there is evidence of a retention of sulphur even normally, for on feeding cholalic acid to dogs he could demonstrate that the amount of bile sulphur is at once increased, whereas the administration of cystin *per se* is without effect.

The question now arising was: What will happen if at this stage cholalic acid is given? The result is seen in the first row of analyses of Table III. This test was followed at once by one in which the patient received 1.5 grm. of cholalic acid and 1.5 grm. of cystin on the same day, both given simultaneously in divided doses of 0.25 grm. each, every hour. On this day the administration began at 12 M. and was continued until 5 P. M. Then follow two days in which neither cystin nor cholalic acid was given, and after this a repetition of the test, with this difference, however, that the cystin and cholalic acid were not given simultaneously.[28]

The results are seen in Table III.

TABLE III.

Date.	Am't	Sp. Gr.	Total S, as S.	Oxid. S, as S.	Neutral S, as S.	% of N. S, as compared with the total S.	Remarks.
23/24	870	1.018	0.5811	0.5710	0.0101	1.7%	1 grm. sod. cholate.
24/25	1000	1.017	0.6380	0.5795	0.0585	5.1%	1.5 grm. cystin and 1.5 grm. sod. cholate.
25/26	1450	1.015	0.8949	0.8265	0.0684	7.6%	
27/28[29]	1250	1.018	0.9370	0.8396	0.0974	10.3%	1 grm. cystin A. M. and 1.5 grm. sod. cholate P. M.
28/29	750	1.023	0.6310	0.5942	0.0368	5.8%	1 grm. cystin and 1.7 grm. sod. cholate.
29/30	1000	1.017	0.8026	0.7304	0.0722	8.9%	

A comparison of the first row of figures with the results obtained on the preceding day, shows that there has been a still further drop of the oxidized sulphur and that the neutral sulphur has fallen to 1.7 per cent of the total—the lowest figures in the entire series. This result finds its logical explanation in v. Bergmann's analogous examination, in which the bile-sulphur elimination was studied (v. s.). Our investigation thus forms the counterpart to that of v. Bergmann and supplements it. It supports the assumption that even normally there is a retention of neutral sulphur in the body, which is eliminated, in part at least, as taurocholic acid, providing that a sufficient amount of cholalic acid is available.

The studies with cystin and cholalic acid, which now follow, were undertaken for the purpose of ascertaining to what extent the cholalic acid is capable of preventing the complete oxidation of the administered cystin. In the first test, as indicated above, the cystin and cholalic acid were given simultaneously. As the cystin sulphur elimination had previously occurred, not in the same, but in the second twenty-four hours, while the excretion of the cholalic acid takes place earlier, there was a possibility that the effect would be essentially the same as if cystin had been fed alone. The result is very interesting. We find that during the first twenty-four hours the elimination of the oxidized sulphur is practically the same as on the previous day, and that the neutral sulphur is still below the average normal, although it has risen somewhat. On the 26th the neutral sulphur was still normal, but the oxidized sulphur had now risen to 0.8265, as compared with 0.6687, the average of the normal days. We thus find that there has been a gain of 0.1578 grm., while in the corresponding previous test with the same amount of cystin given alone 0.2809 was eliminated above the average normal. As 1.5 grm. of cystin contain 0.39 grm. of sulphur, there must either have been a considerable retention, or an elimination through other channels. v. Bergmann's feeding experiments with cystin and cholalic acid in dogs, to which reference has repeatedly been made, can scarcely leave any doubt regarding the fate of the excess of sulphur in this case. That an increase occurred at all may be owing to the fact that too little cholalic acid was given to combine with the entire quantity of cystin to form taurocholic acid, or that the cholalic acid had not been given at the right time. To investigate this possibility the next examination was so modified that the man only

[28] Cholalic acid, as such (viz. as sodium cholate) is in man as in dogs, borne without any ill effects.

[29] The urine from the 26th to the 27th was unfortunately thrown away.

received 1 gramme of cystin, which was given in doses of 0.25 grm. at 8, 9, 10 and 11 A. M., while no cholalic acid was administered until 7 P. M. From this time until the following morning at 7 he was given 1.5 grm., viz.: 0.5 at 7 P. M., 0.25 at 8 and 9 P. M., and 0.5 at midnight. It was hoped that in this manner it would be possible to cause the elimination of a considerable amount of cystin sulphur through the bile, and that correspondingly low values would be found in the urine. The result, however, was different. For we find that the oxidized sulphur had risen 0.1709 grm. beyond the average, and that the neutral sulphur also was somewhat higher than usual, viz., 0.030 grm. In other words, 0.20 grm. of the 0.26 grm. of cystin sulphur had reappeared in the urine, and as usual largely in completely oxidized form. The reason of the appearance of the cystin sulphur in the urine of the same twenty-four hours within which it was fed was this time probably due to the fact that it was all given within the first four hours of that day.

In the next examination, which was unfortunately, but of necessity, the last in the present case, 1 grm. of cystin was given in two doses of 0.5 grm. each, at 2 and 3 P. M. The administration of cholalic acid began at 5 P. M. From that time off the man received 1.72 grm. until midnight. The result is the following: Within the same twenty-four hours no increased amount of sulphur was eliminated in the urine, either in oxidized or non-oxidized form. On the contrary, the values are rather lower than normal. The following day the oxidized sulphur has increased to 0.7304 and the neutral to 0.0722: If we refer the total increase over the previous day to the administered cystin, we find that 0.17 grm. of the cystin sulphur has appeared in the urine, viz., 65.3 per cent, so that we may assume that 35 per cent approximately was eliminated through other channels. This value, we believe, is really a minimal value. Comparison with the average amount of oxidized sulphur for the normal period would give a much higher figure. The fairest conclusion probably would be based on a comparison of our normal values as one group, with the second series embracing the feeding tests with cystin alone, and the third in which cystin and cholalic acid were fed together. Such an analysis would show the following:

During the cystin days (18/19-22/23 incl.) 4.0288 grms. of sulphur were eliminated in the urine. During the same period 5 times 0.7353 (average amount of total sulphur), plus 0.26 plus 0.39 grm. of cystin sulphur, *i. e.*, 4.3265 grms. in all, should have been eliminated, if all the cystin sulphur had been excreted through this channel. We find a deficit of 0.2977 grm. which must have been removed in some other manner. A similar calculation will show that during the cystin cholalic acid period only 4.4846 instead of 5.3218 appeared in the urine, *i. e.*, there is a deficit of 0.8372 as compared with 0.2977 of the cystin period alone. This represents 91.2 per cent of the entire amount of cystin sulphur which has been fed during this period. There can thus be no doubt that the administration of cholalic acid will normally prevent the oxidation of a not inconsiderable amount of cystin sulphur to urinary sulphates, and we thus see again that our experimental results indirectly confirm those reached by v. Bergmann, who noted a corresponding increase of the bile sulphur in his feeding experiments in dogs. Whether or not it would be possible to prevent the oxidation of ingested cystin to urinary sulphates altogether by the administration of larger amounts of cholalic acid remains to be determined. To do so in the human being did not seem justifiable. That it is essential in such investigations to consider the time relation in the administration of the one in reference to the other is clearly demonstrated by our experiments.

To sum up, we believe we have shown:

1. That in the human being the administration of cystin by the mouth does not lead to a material increase in the elimination of the neutral sulphur, but that 53 per cent approximately appears in completely oxidized form.

2. That a portion of the ingested cystin is eliminated through other channels.

3. That the administration of cholalic acid *per se* causes a moderate decrease in the amount of urinary sulphur, which largely affects the neutral sulphur.

4. That the administration of cholalic acid will prevent the oxidation to urinary sulphur of a very considerable portion of cystin administered at the same time.

In view of v. Bergmann's experiments and our own studies, we conclude that a certain amount of the cystin liberated during the normal metabolism of the body is eliminated in the bile in combination with cholalic acid as taurocholic acid, while the remainder appears in the urine in completely oxidized form.

With these data given, it seemed of interest to ascertain in what manner the *cystinuric* individual would react to the administration of cholalic acid. The results follow in the second series of investigations.

SERIES II.

The cystinuric individual was a man, æt. 42, who entered the hospital for purposes of study only. He was not ill at the time, barring some pain in the back, from which he had suffered more or less for a number of years. This pain bears the character of lumbago. A definite history of renal calculus cannot be made out. Early in January of the present year he spoke of having had very severe pain in the region of the kidneys on both sides. At the time he had influenza. He has never passed blood or gravel. He is a large eater and a fairly steady drinker. His weight is usually about 183-185. There is distinct arterial thickening, but beyond this physical examination reveals nothing of note.

The cystin was discovered in the man's urine in July, 1899, when he first came under observation at the Johns Hopkins Hospital, suffering from an attack of febricula. His case is briefly referred to in the collective report on cystinuria by one of us, which was published in January, 1900.[*] At that time Dr. Amberg examined the man's

[*] Simon, C. E.: Cystinuria and its Relation to Diaminuria, Amer. Journ. Med. Sci., Jan., 1900, p. 39.

urine for diamins with negative result. From the feces a small amount of a benzoylated product could be obtained, which was not sufficient, however, for identification. An examination of the urine of the man's children was negative for cystin, but in one a marked sulphur reaction was obtained.

Several examinations of the man's urine have been made since that time. Cystin could always be demonstrated microscopically and separates out spontaneously without the addition of acetic acid. The amount was variable and at times very large. In the urine of the children we also could not demonstrate any cystin, but we noted the marked sulphur reaction, which Dr. Amberg had observed in one of the boys. An examination for diamins, in which ten liters of urine were benzoylated, proved negative; a single fecal examination in the same direction also led to no positive result.

The man's diet, while under observation in connection with the present series of examinations, was constant (see above). During the first three days no cholalic acid was given. On the 28th he received 0.6 grm. in divided doses of 0.1 grm. each, one capsule every two hours; the following day 0.9 grm. was given, and on the next 1.5. Then follow three control days, and after this 5 days on each of which the man received 2.0 grms., in divided doses distributed over the hours from 8 A. M. to 8 P. M. Aside from the bitter taste no unpleasant results were noted. The patient consumed a large amount of water during the entire course of the investigation, and passed correspondingly large amounts of urine (see Table IV). As cause of his thirst he mentioned the bitter taste of the sodium cholate. But as the figures in the table show, the polyuria existed already before the administration of the cholate began and continued during the control days. Possibly the withdrawal of his beer may be of moment.

Unfortunately, we have only one day of satisfactory analyses for the three-day period preceding the administration of the sodium cholate; these were obtained on the second day. The urine of the first day was thrown away, and on the third day other analyses showed conclusively that the collected amount did not represent the entire output of the twenty-four hours. The fact that we only had the single set of analyses for this period seemed at first a serious deficiency, but, as will be seen, the cholalic acid was absolutely without effect upon the sulphur metabolism of our individual, so that we did not deem it necessary to extend the study of "normal" days at that time." The results follow:

TABLE IV.

Date. I. '04	Amount.	Sp. Gr.	Total S, as S.	Oxid. S, as S.	Neutral S, as S.	% of N. S. compared with total S. (total = 100).	Remarks.
25/26	Lost						
26/27	2280	1.015	0.9250	0.6703	0.2547	27.4	
27/28	Incomplete collection					24.8	
28/29	2500	1.012	0.5942	0.5248	0.0694	11.6	0.6 Sod. cholate
29/30	1700	1.012	0.5411	0.4260	0.1151	21.2	0.9 " "
30/31	3480	1.009	0.9102	0.5300	0.3802	41.7	1.5 " "
31/1	3450	1.007	0.7142	0.4258	0.2884	40.3	
II.							
1/2	3480	1.008	1.0033	0.3896	0.6137	61.1	
2/3	3245	1.008	0.7062	0.5906	0.1156	16.3	
3/4	3250	1.008	0.6358	0.6059	0.0299	4.7	2.0 Sod. cholate
4/5	3400	1.008	0.5850	0.3668	0.2182	36.9	2.0 " "
5/6	4720	1.006	0.5503	0.3596	0.1907	35.4	2.0 " "
6/7	3800	1.008	0.6771	0.5807	0.0964	14.2	2.0 " "
7/8	4970	1.007	0.8112	0.5417	0.2697	33.9	2.0 " "

The most striking feature of this table is the inconstancy of the results from day to day. On the 27th we find 0.6703 grm. of oxidized sulphur. This corresponds quite closely to our average normal value in the first case. On the 29th there is a drop to 0.5248, which coincides in point of time with the administration of the 0.6 grm. of cholalic acid. The next day there is a further drop to 0.426, which might be referred to the continued administration of cholalic acid. As the neutral sulphur on the day before had fallen to normal, the inference suggested itself that the cystinuria might actually be associated with, even if not dependent upon, an insufficient production of cholalic acid. On the 31st, however, we find that in spite of the still continued administration of cholalic acid in increased amount there is an abrupt ascent of the neutral sulphur to 0.3802, *i. e.*, to a higher value than was noted on the normal day (the 26th). The lower oxidized sulphur values during these days, as compared with the "normal" day, thus do not indicate as in our control individual that the difference in amount is eliminated through other channels. With the exception of the 28th, the neutral sulphur goes up as the oxidized sulphur goes down, and vice versa.

During the three normal days which follow the three cholalic acid days the neutral sulphur fluctuates between 16.3 and 61.1 per cent of the total sulphur. Then follows the second cholalic acid period, in which the man received 2.0 grms. daily. The results on the 4th again suggest an effect on the part of the cholalic acid analogous to what occurs in the normal individual, but the values which follow are so variable as to render the conclusion that the cystinuria is the outcome of an insufficient production of cholalic acid, quite improbable.

The fluctuations in the sulphur elimination which we noted in our case seem at first quite surprising, but are after all perfectly analogous to what occurs in the bile. Stadelmann already noted the great variations in the daily elimination of all the constituents of the bile, and in v. Bergmann's series the normal sulphur values varied between 0.028 and 0.062 grm. That these fluctuations are the expression of a temporary retention alternating with periods of increased elimination can scarcely be doubted. We have seen evidence of this in our normal individual.

Our studies thus show that while the administration of cholalic acid in the non-cystinuric individual leads to a diminished elimination of the sulphur in the urine, this does not occur in the cystin subject. This would suggest that in the cystinuric individual taurocholic acid is possibly not formed at all, in which case we would be forced to assume either that all the sulphur liberated in the body is eliminated in the urine, or that a portion is excreted in the bile in a form different from taurocholic acid.

" On a subsequent occasion the percentage neutral sulphur values, as compared with the total sulphur on three consecutive days were 29.2, 29.4 and 35.6. The absolute figures were 0.2367, 0.1517 and 0.1774 grm. S.

Unfortunately there are no analyses of the bile of cystinuric individuals available to determine this point. To draw inferences from a comparison of average total sulphur values in the urine of the cystinuric as compared with the non-cystinuric individual would be hazardous, owing to the fact that in man the elimination of sulphur in the bile is rather low. Taking 0.39 per cent of sulphur, given by Pfaff and Balch,[1] as an average value for dried human bile, and 8.57 grms. as an average amount of solids, this would correspond to 0.0334 grm. of sulphur eliminated in the bile in twenty-four hours. This figure is manifestly too low to warrant a comparison of average total sulphur values in the case of the urine. From the fact, however, that in man the amount of biliary sulphur is so small, *we may be warranted in assuming that the elimination of the katabolized sulphur through this channel is of secondary importance only, and that accordingly the presence of more or less cholalic acid (within normal limits) would not materially affect the elimination of cystin in the cystinuric, even if the union between the two were possible, which, according to our studies, is not the case. The presence or absence of cholalic acid, hence, does not enter into consideration in connection with the chemical mechanism which is at work in the production of cystinuria.*

We have shown that so far as the formation of taurocholic acid is concerned two views are possible. Either that the cystin is first oxidized to taurin and that this then combines with cholalic acid, or that the cystin unites with cholalic acid directly and that the resulting product is then oxidized to taurocholic acid. As the formation of cholalic acid is only known to occur in the liver, the cystin in the second case would under ordinary conditions have to reach that organ as such, and we should accordingly expect that it would be possible to demonstrate the presence of cystin in the blood. This, however, has never been accomplished. If we accept the first possibility, on the other hand, we may imagine that the primary oxidation occurs already in the tissues at large where the liberation of cystin takes place. In this case we should expect to find evidence of such primary oxidation in the presence of taurin, for example, outside of the liver. As a matter of fact, taurin has been found in the lungs, the kidneys, the muscle tissue, in the spleen, in the adrenal glands, etc., of various animals.

That a transformation of this order would be effected by intracellular enzymes can scarcely be doubted. Direct experiments with the various tissues at large have thus far only been made in the case of the liver by Blum,[2] who records that on mixing cystin with defibrinated blood and finely hashed liver, and allowing the mixture to stand for seven hours at 37° C., no taurin was obtained. Blum's experiment we do not regard as conclusive, however, as ordinary mechanical comminution may not suffice to liberate the intracellular ferments which would be concerned in the oxidation of cystin to taurin with the coincident loss of carbon dioxide. More detailed experiments in this direction are now under way in Dr. Simon's laboratory, and upon these we expect to report on a future occasion.

[1] Pfaff, F. and Balch, A. W.: Journ. Exper. Med., 1897, vol. II, p. 49.

[2] L. c.

In conclusion, we wish to express our indebtedness to Dr. Wm. Osler for the kind interest which he has taken in our work and the facilities which he has placed at our disposal.

In my previous papers on cystinuria (Amer. Journ. Med. Sci., 1900, Vol. CXIX, p. 39, and *ibid.*, Vol. CXXIII, p. 838, the last in association with Dr. W. M. Lewis), I have given references to 112 cases. Since that time I have found records of additional cases as follows: Gamgee, A case of cystinuria with formation of calculi, Lancet, 1901, I, p. 470. Percival, A., Un caso di cistinuria, Clin. Med. Ital., 1902, Vol. XLI, p. 50. Gilbert, G. A., Report of a case of cystinuria, Chicago Clin., 1900, Vol. XIII, p. 177. Abderhalden, E., Familiäre Cystindiathese, Zeit. f. Phys. Chem., 1903, Vol. XXXVIII, p. 557 (five cases). Riegler, Ein interessanter Fall von Cystinurie und Cystinsteinen, Wien. Med. Blätter, 1904, No. 3 (Ref. Biochem. Centralbl., 1904, Vol. II, p. 373). Schölberg, H. A., and Garrod, A. E., Ein Fall von Cystinurie mit Diaminurie, Lancet, 1901, II, p. 526, previously reported by Sadler, *ibid.*, 1901, I, p. 470. One of the cases previously referred to by Garrod in a note to me has since been published by Cammidge, P. J., Cadaverin im Harne in einem Fall v. Cystinurie, Lancet, 1901, II, p. 592. In addition, Dr. Garrod has kindly drawn my attention to the following cases in the earlier British literature: Bence Jones, Trans. Pathol. Soc., 1848-50, Vol. II, p. 237. Risdon Bennett, *ibid.*, 1850-2, Vol. III, p. 383. Church, W. S., *ibid.*, 1869, Vol. XX, p. 240. Sir Henry Thompson, *ibid.*, 1870, Vol. XXI, p. 272. C. Heath, *ibid.*, 1876, Vol. XXVII, p. 360, and XXIX, p. 154. Shattock, S. G., *ibid.*, 1879-80, Vol. XXXI, p. 182. Ord, W. M., *ibid.*, p. 384. Bowlby, A. A., *ibid.*, Vol. XL, p. 182, and Jacobson, Trans. Clin. Soc., 1891, Vol. XXIV, p. 170. Adding these 19 cases to the 112 previously collected, there are now 131 of which notes exist in the literature.

S.

NOTES ON NEW BOOKS.

Elements de pathologie et de clinique chirurgicales. By DR. LEON MOYNAC (DE BAYONNE). Eighth edition, three volumes. Illustrated by 134 engravings. *(Paris: G. Steinheil, 1903.)*

The fact that a book has reached its eighth edition is certainly evidence of a continued demand for its publication, although we do not feel sure that it is, as the writer claims in his preface, a guarantee of its established usefulness. The arrangement of subject matter in the three volumes is very suitable, the first volume being devoted to the surgery of the tissues; the second to that of the brain, the trunk, and the limbs; the third to special surgery.

A large part of the first volume is occupied with fractures, dislocations, and bone lesions, all of which are quite fully discussed; but these subjects suffer especially from a defect which detracts from the value of the book throughout, namely, a

paucity of illustrations. The whole number of these (324) is insufficient for a work of such scope; moreover, they are of small size, and not very clearly printed.

Abdominal surgery, which is considered in the second volume, receives but scant attention, when the extent of its present boundaries is remembered. The subject of appendicitis especially is very cursorily considered, and to American ideas seems much behind the time. Operation, we are told, is indicated only upon the appearance of a tumor, and but one method of incision and removal is given, these being disposed of in less than a dozen lines. We are somewhat surprised to learn that in America the routine treatment of appendicitis, in the absence of operation, is purgation. Abscess in the right iliac fossa is separately considered, although the writer admits that the large majority of such cases originate in the appendix vermiformis.

Surgical affections of the mammary-gland also are very briefly dismissed, only twenty-five pages being devoted to a class of diseases so important and so frequent. Hernia, on the contrary, is considered very fully, the radical treatment of it being warmly advocated.

In these days of specialization and collaboration it strikes us as strange that the highly individual subjects considered in the third volume should be treated by one person, and he the same one who has already treated general surgery. Ophthalmology, otology, and gynecology are generally considered to be the province of their own highly trained specialists, but in this case no assistance has, apparently, been sought in their treatment. No names are mentioned as contributors, and the author makes no acknowledgments, except a few words of thanks in the preface to Mm. Hartmann and Terrier for permission to copy illustrations from their works.

A good many things are well said, and the book is to be commended in that the author never loses sight of the simplicity of style and expression suited to its declared purpose, namely, that of a text-book for students, rather than a reference book for practitioners. As a whole, however, it fails to inspire entire confidence, largely, perhaps, because the treatment of so many and such diverse subjects by one individual cannot but excite a suspicion of inadequacy in some of them. It has the advantage of being well indexed, having both a table of contents for chapters, and an alphabetical index of subjects.

A Surgical Hand-book for the use of Students, Practitioners, House-Surgeons and Dressers. By FRANCIS M. CAIRD, M. B., F. R. C. S. (Ed.), and CHARLES W. CATHCART, M. B., F. R. C. S. (Eng. and Ed.). Twelfth edition with numerous illustrations. *(London: Charles Griffin and Co., Limited; and Chicago: W. T. Keener and Co., 1903.)*

This is a useful little work in which the whole duty of a surgeon is compressed into a volume of such small size that it can be carried in the pocket for constant reference. Nothing is more difficult than to carry compression to such an extent without sacrificing completeness of subject matter or clearness of style. The authors are to be congratulated that they have succeeded well in their present attempt. The illustrations, although small are suitable, and the print is much better than could be expected when it is necessarily so minute.

The Therapeutics of Mineral Springs and Climates. By I. BURNEY YEO, M. D., F. R. C. P. *(Chicago: W. T. Keener and Co., 1904.)*

This work is the third of a series covering the entire field of therapeutics. It is a subject, which has long engaged the writer's attention, and he considers it very thoroughly. The first part of the work, which is devoted to Mineral Springs, classifies them according to the nature of their waters, and then describes the countries which belong under each class. It then proceeds to consider the action, both external and internal, of each class, and finally to discuss the chief springs individually. The second part of the work is concerned with climates, and is arranged under the same general plan.

We have sketched the whole book in outline, because its value to those who need it lies in the extent of information it contains. That this information can be relied upon is guaranteed by the author's reputation. The work is very thoroughly done, and contains many items of interest, and often of service outside of the beaten track, to the invalid condemned to expatriation. We do not need the author's assurance that it represents care and pains in the preparation, for it carries within itself the assurance of both, and we are indebted to him for a fund of reliable information, not only upon the main points at issue, but upon many of the minutiae, a knowledge of which smooths the path of the tourist in search of health.

Mammalian Anatomy with special reference to the Cat. By ALVIN DAVIDSON, PH. D., ex-fellow of Princeton University; Professor of Biology in Lafayette College. With over 100 illustrations made by W. H. Reese from the author's dissections. *(Philadelphia: P. Blakiston's Son and Co., 1903.)*

The principle of this work is that enunciated by Huxley, namely, that it is wiser for a student to begin with the study of vertebrate rather than invertebrate anatomy. The structure of the cat to which the book is devoted, is intended to illustrate the broad outlines of the more important morphologic structures of the Mammalia. It has the defect common to all anatomical text-books of devoting too large space to the skeleton, but the remaining divisions are well adjusted. The descriptions are clear and the illustrations well chosen.

Transactions of the Medical Association of Georgia. Fifty-fourth Annual Session, 1903. *(Atlanta, Ga.: The Franklin Printing and Publishing Co., 1903.)*

A number of papers of greater or less excellence are here brought before the public in excellent form, the paper, type, binding, etc., being well chosen and executed.

One excellent article is by Floyd Willcox McRae, of Atlanta, on "The sin of so-called conservative treatment in diseases requiring prompt surgical intervention." It is a subject of great importance, besides being one which often escapes attention, especially in rural districts. Strangulated hernia and fulminating appendicitis are the two conditions discussed in detail, with force and effect, and the discussion at the close showed his hearers appreciative.

The use of large doses of strychnia in ileus is strongly advocated by R. M. Harbin, of Rome, with the idea that it secures the one great end, namely, the regulation of the bowels without the difficulties incident to other methods.

The vaginal route in gynecology finds a strong advocate in George R. White, of Savannah, who has apparently gone closely into his subject and gives a complete bibliography of it.

A sensible paper by Ralph M. Thomson, of Savannah, on "Criminal Kindness," shows clearly and justly that the indiscriminate feeding of infants should be classed under this head. We cannot quite agree with him, however, that the cheapness of the food eaten by the children of the poor ensures corresponding simplicity and wholesomeness of diet. That it necessarily excludes certain costly dainties is true, but coarseness, lack of variety, and adulteration are counter-balancing evils.

Another useful paper is one by John C. McAfee, of Macon, on "An operation for permanent and quick cure of hemorrhoids, almost bloodless and painless." The writer says that "an anodyne is frequently not needed after the operation and patients invariably tell me that they feel better the day after the operation than the day before." Such testimony is of considerable value,

when we consider the exquisite suffering which patients are forced to endure at present after the removal of hemorrhoids.

A Practical Treatise on Genito-Urinary and Venereal Diseases and Syphilis. By ROBERT W. TAYLOR, A. M., M. D. (*New York and Philadelphia: Lea Brothers and Co., 1904.*)

This volume is an old friend in new garb, being the third edition of a work which has already taken a place—and a creditable place—in American medical literature. The rapid exhaustion of the large second edition proves that the book has shown itself a satisfactory and trustworthy guide for practitioners and students of medicine and invalidates empirically the doubt which obtrudes as to the need of a new volume in this somewhat restricted field of surgery. Taylor's book certainly stands in the first rank of American text books of Genito-Urinary Surgery—along with Keyes, White and Martin and possibly one or two others. It compares favorably, too, with Casper, indeed, for student purposes, is probably superior to it. But, though all of these works are good, none is excellent and that adjective is certainly extravagant in reference to the volume before us. The conventional material for works of this sort—gonorrhea in all its aspects, stricture, syphilis, etc., is fully, lucidly and usefully treated and the text is richly illustrated by pictures, the majority of which are to be commended for their excellence. A few are particularly good; while several, notably some of the microscopical drawings and a view of a carcinomatous penis, are particularly bad. Dr. Taylor has included in his book, logically we think, the venereal affections of female genital organs and the work is, from the venereal side, a complete one. Two hundred and seventy of the seven hundred odd pages are devoted to syphilis and our author has therefore made genito-urinarian and syphilographer roughly synonymous. This, however, is somewhat contrary to the custom which obtains. Genital and urinary surgery is constantly being more and more emphasized, while genital medicine, so far from forming the main and essential material for genito-urinarians, is being largely shared with dermatologists and clinicians. Text books of genito-urinary surgery have even gone so far as practically to omit all mention of syphilis; and while it would be absurd to insist on the relegation of this protean malady to any one department of medicine, it does seem as though its constant association with and inclusion in genito-urinary surgery ought to have some more logical basis than the frequent occurrence of the initial lesion on the genitals.

Genital surgery has received less complete and less intelligent treatment in the volume before us than genital medicine. We turn for instance instinctively to one of the live surgical subjects and we find prostatic hypertrophy rather scantly considered. A catheter life is strongly advised as long as it is possible or "wise." The perineal operation is dismissed with a small paragraph and no procedure is mentioned but that of Alexander. Suprapubic prostatectomy is said to be the operation of choice in the great majority of cases demanding operative relief, "as the overgrowth can be inspected, hemorrhage readily controlled, and calculi removed without adding any risk to the operation,"—hardly convincing reasons for the preference to perineal prostatectomy to which they equally apply.

One cannot escape the impression that Dr. Taylor has failed to bring to this work the intimate and extensive acquaintance with the recent literature of the subject which is essential to a really first rate text book. We find extravasation of urine, for instance, regarded as always following urethral rupture and no mention made of Albarran's "urinary edema of septic origin," or of Motz's convincing study of the subject with his conclusion as to the inaptness of the conventional term for the condition.

A Text-book of Physiology. By ISAAC OTT, A. M., M. D. Professor of Physiology in the Medico-Chirurgical College of Philadelphia. With 137 Illustrations. Royal Octavo, 563 pages. (*Philadelphia, Pa.: F. A. Davis Company, Publishers.*)

The scope of Professor Ott's work may be judged of by the following extract from the author's preface: "This book has been written at the solicitation of students who have attended my lectures for the past eight years. The aim has not been to write a treatise on the subject but rather an elementary work containing the chief facts of physiology which are necessary to the student who wishes to apply them in the practice of his profession."

Perusal of the work has given to the reviewer an impression which the preface might lead one to expect. The subject-matter is subdivided and handled just as in most of the text-books of physiology of to-day. Perhaps the only distinctive feature is its brevity. Excepting certain sections, *e. g.*, electrophysiology, brevity has been obtained by omission of explanations rather than by the ommission of facts—by empiricism rather than by judicious elimination of all but important topics. This brevity coupled with only too frequent inexact and awkward diction, cannot fail to limit the value of the book from the student's standpoint.

However, the work demonstrates that the author is thoroughly familiar with all of the old and new contributions to the subject of physiology and furthermore that he has at his command a valuable fund of interesting collateral data. And we should not lose sight of the fact that the book has been written at the solicitation of *his* students and therefore in all probability, for his students. The reviewer believes that the work will prove of very great value to the author's students when used by them to supplement the author's lectures.

Manual of Materia Medica and Pharmacy. Specially designed for the use of Practitioners and Medical, Pharmaceutical, Dental and Veterinary Students. By E. STANTON MUIR, PH. G., V. M. D. Instructor in Comparative Materia Medica and Pharmacy in the University of Pennsylvania. Third edition, revised and enlarged. Crown 8vo. 192 pages. (*Philadelphia, Pa.: F. A. Davis Company, Publishers, 1914-16 Cherry Street.*)

This book is of such a character as to be generally useful, but like other books of its kind, the tendency is to condense the subjects too much. It is divided into three parts.

The first part treats of botany or rather of botanical terms, and evidently is intended to explain botanical descriptions to those who have not studied the science. It is the merest outline.

The second part is devoted to drugs and chemicals, the important points of each being well arranged. The arrangement is an alphabetical one. If it were different the book would be of more value to the student.

In the third part which treats of Pharmacy and Pharmaceutical Preparations, some of the descriptions of the classes of Official Preparations are much too brief and misleading to be of use to one not familiar with Pharmacy. For instance, on page 149, under Emulsions, the author says, ". . . . They are prepared by triturating the medicinal agent with the gum or sugar and slowly adding the water . . ." J. L. W.

Golden Rules of Psychiatry. By JAMES SHAW, M. D. *Golden Rule Series, No. V.* (*Bristol: John Wright & Company.*)

This vest pocket volume contains a wonderful amount of information clearly and tersely expressed on the symptoms of mental diseases as they are usually encountered by the general practitioner. While the tabloid system is not to be recommended, when

applied to gaining knowledge, to those not familiar with the insane, this is a means of reviewing knowledge previously acquired. From a perusal of it the student will gain a great many points which will be of value in assisting to fix in his memory the knowledge which he gains at lectures and clinics. The author is to be congratulated on having put so much information into such small compass. W. R. D.

A System of Practical Surgery. By PROF. E. VON BERGMANN, PROF. P. VON BRUNS and PROF. J. VON MIKULICZ. Volume III. Translated and edited by WILLIAM T. BULL, M. D., Professor of Surgery, Columbia University, and CARLTON P. FLINT, M. D., Instructor in Minor Surgery, Columbia University, New York. Surgery of the Extremities. (*New York and Philadelphia: Lea Brothers & Company, 1904.*)

This system of surgery is so well known that it seems almost useless to discuss it. For the benefit of those to whom this translation, however, may be new, a brief sketch of the contents may not be uninteresting.

The third volume of this edition is devoted to the Surgery of the Extremities. The anatomical divisions of the parts are made to serve as a basis of classification. Each section is taken up in the same manner. The first section deals with the malformations, injuries and diseases of the shoulder and upper arm. In the same way the elbow and forearm, wrist and hand, hip and thigh, knee and leg, and ankle and foot are treated.

Probably the most interesting section is that upon the hip and thigh. In this part the various bloodless methods of reduction of congenital dislocation of the hip joint are given in so clear and concise a manner that the reader easily grasps the salient points of each method.

The value of the book is enhanced by an extensive bibliography at the end of each section.

The illustrations are numerous and for the most part good. This, however, cannot be said of the X-ray productions. They are few in number and are not as good as one would expect to find in such a work.

The translators, broadly speaking, have followed the text closely. It is a matter of regret, however, that they should have thought it wise to omit several chapters. The work is one that should be in the hands of every surgeon.

A Preliminary Report on a Parasite Found in Persons Suffering from Enlargement of the Spleen in India. LIEUT. S. R. CHRISTOPHERS. Scientific memoirs by the officers of the Medical and Sanitary Departments of the Governments of India. New Series, No. 8. (*Calcutta: Office of the Superintendent of Government Printing, 1904.*)

This monograph of 17 pages is a concise, clearly written report, by the author, of his investigation of the disease with which the so-called Leishman-Donovan bodies have been found associated. The protozoan parasite was first described by D. D. Cunningham in 1885, but escaped any general notice until rediscovered by Leishman in May, 1903, and further described by Donovan in July of the same year. Laveran and Mesnie have named the parasite the Piroplasma donavani—inappropriately the author thinks, as he finds but slight resemblance between it and other members of the genus.

The disease in which the parasite is found prevails in Madras, Calcutta, and other parts of India and is probably identical with the disease known as "*kala azar*" in Assam. It is characterized by (1) great enlargement of the spleen, (2) emaciation, (3) irregular pyrexia uninfluenced by quinine, (4) abdominal symptoms (diarrhea and dysentery), and sometimes by œdema of the feet.

Post-mortem one finds a large, firm, non-pigmented spleen, and as a rule large ulcers in the large intestine, which often perforate leading to death from peritonitis. Except for small hemorrhages in the peritoneum and arachnoid, the other changes are those common to febrile diseases. The parasites are not found in the circulating blood, but in the spleen and liver, and in the large intestine about the ulcers. In these situations they usually are found in macrophages. Red blood cells do not appear to be attacked. The parasite is round or oval in one aspect, somewhat pyriform in the other and is characterized by the presence of two chromatin masses and a vacuolated protoplasm. Sexual forms have not been distinguished. Reproduction takes place by division.

The author describes a modified Romanowsky stain by which he has successfully stained the parasite in section.

Second Report of the Anti-Malarial Operations at Mian Mir, 1901-1903. LIEUT. S. R. CHRISTOPHERS. Scientific Memoirs, etc. New Series, No. 9. (*Calcutta: Office of the Superintendent of Government Printing, 1904.*)

The author reviews the work of Captain James, I. M. S., in 1901 and 1902 and of himself in 1903, in which an endeavor was made to reduce the prevalence of malaria among the troops at Mian Mir by procedures directed against the *anopheles* mosquitoes, of which seven varieties were found. The campaign was carried out along the usual lines of drainage; of clearing of irrigation ditches of vegetation, and of "oiling" the surface of pools and ditches, but did not attain to the success claimed by others. For "in Mian Mir almost complete absence of breeding was ensured to a distance of over half a mile, but adults (*anopheles*) still appeared in large and increasing numbers in the area." The malarial season, however, seemed to be postponed and thereby shortened. The author attributes the failure of the operations to the entrance of mosquitoes from without the area supervised, and is of the opinion that the operations "were not those best adapted to the eventual reduction of malaria," believing "that gradual, but permanent improvement in the health of stations by well-directed reforms, whenever these can be carried out, will in the end yield the best return."

Infant Feeding in its relation to Health and Disease. By LOUIS FISCHER, M. D., Visiting Physician to the Willard Parker and Riverside Hospitals, New York City. Third edition. (*Philadelphia: F. A. Davis Company, 1903.*)

The book has been revised and enlarged until it now appears in its third edition, a volume of 357 pages which include a bibliography and very good index. The anatomy, chemistry and physiology forming the foundation of rational infant feeding find consideration in the early part of the book. While the treatment of these subjects includes all the points recognized as essential, the text is not so full as could be wished and often suggests it is no more than notes the author has made in going through the literature.

The clinical side of the work is not open to this criticism. Practical feeding is thoroughly considered, and well illustrated with cases from the author's own experience.

The book will prove useful to those who have occasion to direct the nourishment of young children.

Clinical Treatises on the Pathology and Therapy of Disorders of Metabolism and Nutrition. By PROF. DR. CARL VON NOORDEN. Authorized American Edition translated under the direction of BOARDMAN REED, M. D., Philadelphia. Part V. Concerning the effects of saline waters (Kissingen, Homberg) on Metabolism. (*New York: E. B. Treat & Co., 1904.*)

An essay of eighty-nine pages bearing close resemblance to a testimonial for Kissingen water, and quite unworthy of the guise of science which it has been given.

BOOKS RECEIVED.

Adolescence. Its Psychology and its Relations to Physiology, Anthropology, Sociology, Sex, Crime, Religion and Education. By G. Stanley Hall, Ph. D., LL. D. Two volumes. 1904. 8vo. D. Appleton and Company, New York.

The Mattison Method in Morphinism. A Modern and Humane Treatment of the Morphine Disease. By J. B. Mattison, M. D. 1920. 12mo. 40 pages. E. B. Treat & Company, New York.

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